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SLEEP AND WAKEFULNESS HANDBOOK FOR FLIGHT MEDICAL OFFICERS,(U)
1982 A N NICHOLSON, B W STONE

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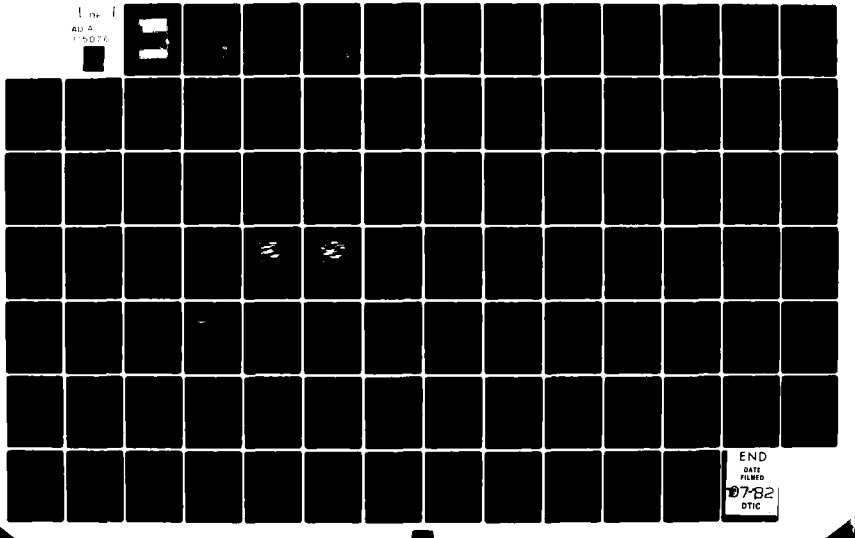

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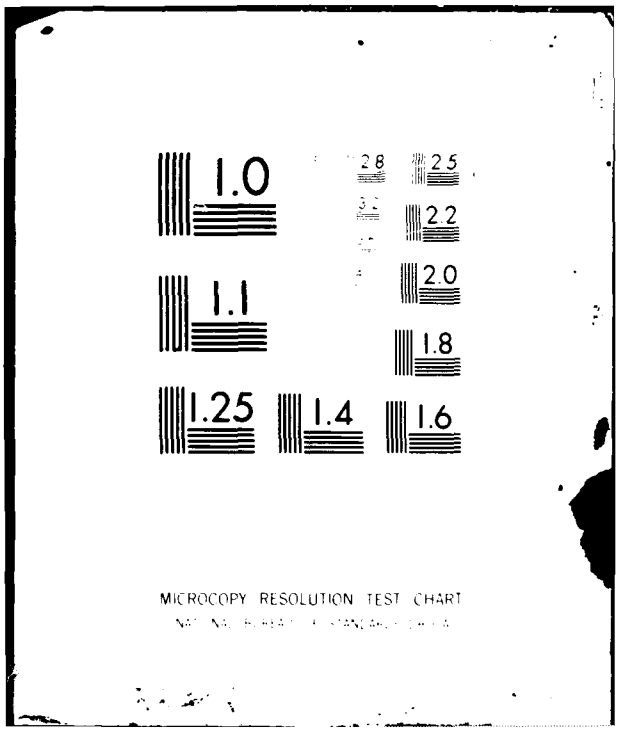
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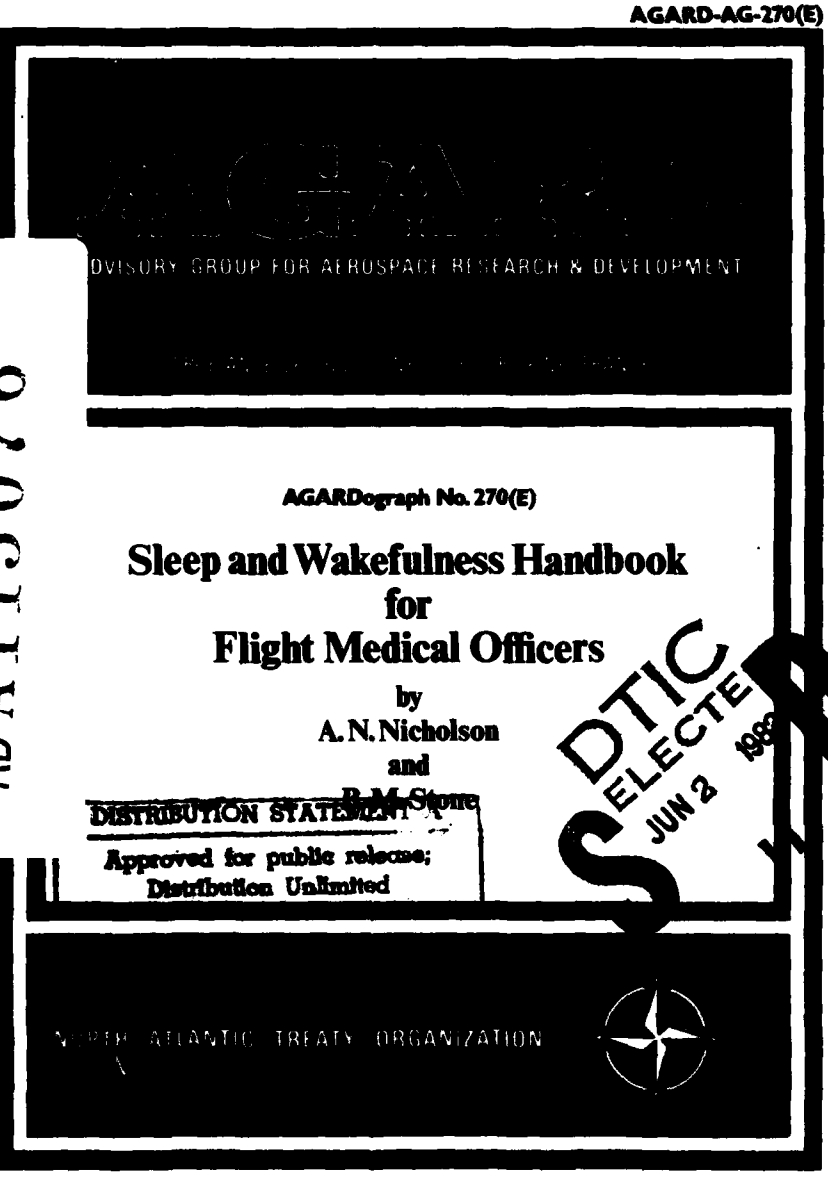

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Sleep and Wakefulness Handbook for Flight Medical Officers

by
A. N. Nicholson
and
P. M. Stone

AGARD-AG-270 (E)

NORTH ATLANTIC TREATY ORGANIZATION

ADVISORY GROUP FOR AEROSPACE RESEARCH
AND DEVELOPMENT

(ORGANISATION DU TRAITE DE L'ATLANTIQUE NORD)

AGARDograph No.270 (E)

SLEEP AND WAKEFULNESS

HANDBOOK FOR FLIGHT MEDICAL OFFICERS

by

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1982

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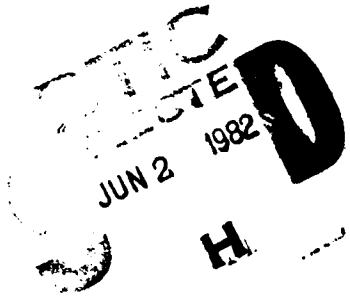
FOREWORD

by

Air Marshal David W.Atkinson, QHP, RAF
Director General Medical Services
Royal Air Force

This handbook on sleep and wakefulness related to aircrew and the aviation environment has been sponsored by the Advisory Group for Aerospace Research and Development. Recently there has been considerable interest in the problems which arise from the inevitable irregularity of work in aircrew, and this concerns both civil and military operations. Centres in the behavioural sciences have been particularly involved with the problem, and over the past ten years or so have contributed through the Aerospace Medical Panel to many activities related to aircrew workload. It is the contribution of these centres which has been distilled in a detailed but clear and practical handbook for Flight Medical Officers on which the authors are to be congratulated. It is hoped that it will help medical officers in their approach to the operational problems associated with irregular work and rest and in their management of aircrew.



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We are also grateful to Miss Adrienne Kern who prepared the manuscript.

CONTENTS

CHAPTER 1

ALERTNESS AND SLEEP

The ability to sustain performance is especially important in aviation. Alertness is the major determinant of sustained performance, and is influenced not only by the duration of each period of wakefulness and by the inherent circadian rhythmicity of man, but also by his need for sleep. There can be no doubt that sleep is essential to alertness, and alertness to continued effectiveness. However, though the adverse effects of sleep loss extending beyond 24 hours are well established – even if not widely accepted – those related to irregularity of sleep, which are particularly relevant to air operations, are less clear. The difficulty in establishing such changes may merely reflect the complexity of the problem. At one time there was uncertainty concerning impaired performance with sustained sleep loss, and it could well be that the effects of irregular sleep are equally subtle, though of a different nature.

The aeromedical specialist is frequently involved in the problems of prolonged work and disturbed sleep, and the whole syndrome is often referred to as fatigue. It is the inevitable result of sleep disruption, deficit or deprivation, and any sleep loss potentiates other fatigue-inducing factors associated with prolonged work. As a complaint it probably indicates sleep deficit, and it is likely to precede impaired performance. Though difficult to define, fatigue involves a subjective appreciation of tiredness, possibly impaired psychomotor performance but certainly momentary lapses of attention. As sleep deprivation continues the individual's performance may be largely that of a reasonably acceptable level of efficiency broken by frequent lapses of attention.

There are many reasons why the importance of deficits associated with long periods of work are underestimated and often disregarded. Subjectively, at least, individuals may be more easily satisfied with less than adequate performance, and errors remain uncorrected – even though they are recognised from time to time. Aversion toward a task may be minimised, at least temporarily, as the individual mobilises his resources to complete the problem. In this way, decrements in performance on the

primary task are avoided, though other elements which are erroneously believed to be less critical are impaired. Further, though the individual may lose flexibility of approach and ability to perceive or adjust to new aspects of a problem, this would only be detected if the focus of performance was being studied.

DISTURBED SLEEP

As far as sleep loss is concerned there are equally a variety of reasons why it may be difficult to accept that it will lead to impaired performance. In many situations sleep loss is less than believed, and tests of performance may not be relevant to the nature of the deficits which arise. The effects of sleep loss vary widely. Interest and motivation are important variables in predicting whether performance will be altered. Interesting tasks involving relatively simple motor skills are resistant for periods as long as 60 hours, but routine monotonous tasks show a rapid and severe decrement after 24 hours without sleep. Motivation may counteract some of the sequelae of sleep loss, though this may be less effective in the very high workload situation of intensive operations.

It is well established that skills such as vigilance are dependent on adequate sleep, but other skills less amenable to measurement are also affected. Indeed, the preservation of behavioural integrity, particularly in those who exercise command, is likely to be equally critical, if not more so, to the success of an operation. In this way changes in mood such as increased hostility, irritability and inability to concentrate, which are often experienced with only one night's sleep loss, may have an importance far beyond those of the loss of discrete and relatively easily measured skills.

The effects of disturbed sleep on performance may be approached in three ways. Total sleep loss is absence of sleep for at least 24 hours, while partial sleep loss is a reduction in the usual amount of sleep over 24 hours. The third category, irregularity of sleep, implies a fragmented pattern of work and rest which is also likely to involve sleep loss. Clearly, there is overlap between partial sleep loss and irregularity of sleep, but it is useful from an operational aspect to consider them separately. Irregularity of work and of rest rather than a reduction in the duration of nocturnal sleep is the dominant issue in air operations.

TOTAL SLEEP LOSS

Under operational conditions there is always doubt concerning the nature of the sleep loss. It is difficult to avoid very short periods of sleep, and so to be sure of the completeness of the deprivation. Indeed, in experiments involving long periods of wakefulness – say 72 hours, microsleeps and drowsiness easily occur. They become more frequent as the period of attempted wakefulness continues, and if not immediately aroused the individual will progress rapidly through the normal stages of sleep. So-called total sleep loss could involve a change from the normal sleep pattern into that of microsleeps and drowsiness. However, there is no evidence that microsleeps ameliorate the impaired performance which arises from sustained wakefulness, or that drowsy sleep, the transition between wakefulness and sleep, preserves performance.

Though under field conditions it may be difficult to allay sleep, complete absence of sleep has probably been achieved in laboratory experiments. Nevertheless, early studies did not consistently detect impaired performance – though changes in mood were obvious. However, as the approach to measurement of performance became more sophisticated, it was realised that absence or delay in response rather than accuracy were the sequelae, and so the importance of adequate sleep to sustained performance was established. Sleep deprived subjects can carry out tasks accurately, but their periods of accuracy become briefer and more infrequent as the deprivation continues. The sequel of sleep deprivation is brief intermittent lapses in performance which increase in frequency and duration, and so impaired performance is seen as missed signals and errors of omission. Memory may also be impaired.

Some situations are more sensitive to sleep loss than others. The longer the task the more obvious are the changes. Loss of a night's sleep may have little effect during the first five minutes of a vigilance task, but deterioration will be obvious when the task is extended to fifteen minutes. Total sleep loss of 50 hours impairs vigilance after three minutes, while after 70 hours vigilance is decreased within only two minutes. The loss of one night's sleep impairs the ability to add after ten minutes, whereas additions may be impaired after only six minutes with the loss of two nights' sleep. Increasing the difficulty will make a task

more sensitive. When an addition is required every two seconds no change even after two nights' sleep loss can be established, but when the speed of addition is increased to one every 1.25 seconds, effects are usually observed. Loss of sleep for 24 hours impairs the acquisition of information and the recall of newly learned material, and there is a drop below 40% of baseline levels of performance at such tests toward the end of a 48 hour period of continuous work without sleep or naps.

It is unlikely that proficiency on complex and prolonged tasks can be maintained at acceptable levels over periods of 20 hours without rest. Long, repetitive and boring tasks, complex tasks, tasks which involve short-term memory, newly acquired skills and those not well practiced are particularly sensitive to sleep deprivation, though self-paced tasks and relaying of information on performance to the individual will tend to minimise the effect. It is possible that with some skills even shorter periods of prolonged working would lead to impaired performance. There may also be less specific, but, even so, equally important sequelae. Susceptibility to disorientation may be increased, scanning ability may be reduced and the ability to read charts may be affected. Perhaps, most important of all, judgement and mood will be impaired.

Nevertheless, recovery from continuous sleep deprivation is rapid, and usually reached within 15 hours. After 36 48 hours of continuous work without sleep, baseline performance is regained after 12 hours of rest, although mood changes persist. Further, no matter how long the period of wakefulness, there is a dramatic improvement in performance and behaviour after only one night's sleep. Indeed, subjects deprived of four nights' sleep reach high levels of performance immediately after one recovery night, though more sleep is needed to restore performance to baseline level, and adverse mood changes will persist beyond the sleep of a single night.

PARTIAL SLEEP LOSS

It is unlikely that the reduction of any particular stage of sleep which may occur in partial sleep loss is specifically associated with impaired performance, but the factors which influence performance with total sleep loss are relevant, even though impaired performance is not consistently related to partial sleep loss. It is true that most subjects appear to function

with minimal impairment during restricted sleep schedules, but many of the tests have been used for relatively short periods, and so failure to detect impairment is not surprising. The loss of only 2.5 hours sleep each night for 2 nights has been shown to impair vigilance the next morning, and it must be assumed that repeated partial sleep loss will lead to impaired performance.

IRREGULARITY OF WORK AND REST

Irregularity of work and rest over several days is also followed by falling levels of performance, and such schedules reveal the adverse effects of the juxtaposition of unfavourable influences. Recent and cumulated sleep loss, together with the fall in performance during the early hours of the morning related to circadian rhythmicity of man, combine during high workload schedules involving irregularity of rest to impair ability, as does the length of the duty period itself. More information is needed about the sequelae of irregularity of sleep and wakefulness with its inevitable accompaniment of, at least, some loss of sleep.

SUDDEN AWAKENING

Another problem is that of efficiency upon sudden awakening. Decrements compared with normal day time values are present just after being awakened from a normal night's sleep. Recovery may be linear for simple, discrete tasks but return to normal working levels may take as long as 20 minutes. Very low performance is encountered on awakening from poor sleep after a stressful period of work which involves sleep loss. More complex tasks require a longer recovery time. The use of alarms does not accelerate recovery, though a few minutes of rest immediately after awakening offsets the decrement of the subsequent performance. Most certainly working in a concentrated fashion after sudden awakening prejudices the capacity to perform effectively, though the decrement in those who have to face such a requirement repeatedly may be less than would be expected.

OPERATIONAL SIGNIFICANCE

There may be some doubt concerning the operational relevance of much of the information which is available on the effects of sleep loss. Indeed, it has been suggested that stable

sleepers are able to maintain performance for long periods of time even with some reduction in sleep time. However, it would be unwise to reject the implications of experimental findings, and it must be realised that the fall in performance associated with circadian rhythmicity is likely to have an additive influence in operations which involve work at times when the individual is usually asleep. Disruption of the sleep-wakefulness cycle with some sleep loss is the problem in operations which extend beyond a single day, and it intensifies, perhaps in a logarithmic fashion, as the duration of the mission is prolonged.

Although, performance depends on complex interactions between task, environment, work schedule and the individual himself, it will be impaired when the subject becomes sleepy. If the individual can be motivated to remain alert sequelae may be minimised, though probably not in very high workload situations. Impaired performance follows sleep loss, and with irregularity of work, particularly relevant to air operations, the adverse juxtaposition of falling levels in performance related to circadian rhythmicity and the immediate and cumulative effects of sleep loss all combine to impair ability during long duty periods. Impaired performance will involve vigilance and memory, but impaired behavioural integrity may be equally, if not more, important in situations where the effective interaction of individuals under stress is vital.

CHAPTER 2

SLEEP

Much of the information available on sleep in man has been gathered in purpose-built sleep laboratories where the electro-encephalogram, electromyogram and electro-oculogram together with other physiological and psychological variables are recorded. Over the years this information has contributed to the present day knowledge of sleep and of its disorders, and of the effects of unusual patterns of work and rest. In many centres these studies are linked to assessments of performance, and the two approaches have helped in understanding the balance between efficacy and adverse effects of hypnotics. In this chapter we deal with the investigation of sleep and of its physiological correlates.

Sleep Electroencephalography

To compare data from different centres the 10 20 electrode system of the International Federation is used. When only one channel is available the C4-A1 or C3-A2 derivation is recommended, and since electrical patterns from homologous areas are generally synchronous, either the right or left side may be selected. However, additional channels, such as P1-T5 and OzPz-03, help in the definition of particular stages of sleep, and are also useful when artifacts or electrode failure occur. In particular, alpha rhythm is better recorded from occipital areas than from a single vertex channel. A typical array of electrodes used in sleep recording is shown in Figure 1. Electrode resistances should not exceed 10 Kohms at the beginning of the recording, and time constants shorter than 0.3 seconds and selective filtering below 20 cycles sec^{-1} should be avoided. A paper speed of 10 mm sec^{-1} is the slowest which will permit easy visual resolution of alpha and sleep spindle frequencies, and a minimum pen deflection of 7 10 mm for 50 microvolt (μv) deflections is necessary, otherwise low amplitude spindles may escape detection.

To avoid confusion between the eye movements seen in rapid eye movement (REM) sleep and other similar signals, at least two channels of electro-oculography are required. The recommended procedure is to record the potential between an

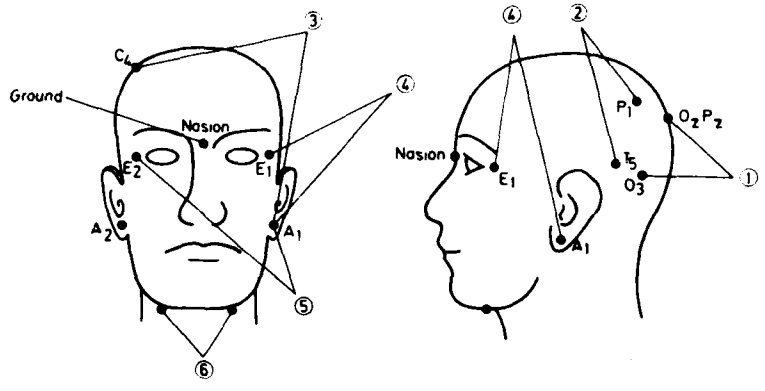

Fig.1 Electrode placements. The electroencephalogram (eeg) is recorded on three channels (C4-A1, P1-T5 and OzPz-03), together with two channels of electrooculography (eog) (E1-A1 and E2-A1) and the submental electromyogram (emg)

electrode approximately 1 cm above and slightly lateral to the outer canthus of one eye and a reference electrode on either the lateral ear lobe or mastoid, and the potential from an electrode 1 cm below and slightly lateral to the outer canthus of the other eye referred to the contralateral ear or mastoid. The reference electrode is the same for both eyes, and this arrangement produces out of phase deflections on the two channels for almost all eye movements. Artefacts usually register as in-phase deflections or are seen on one channel only, and the deflections produced by eye movements are easily recognised. A minimum gain of 7 mm per 50 μv is recommended for eye movement recording, and to detect slow eye movements time constants faster than 0.3 sec should not be used.

The electromyogram is particularly useful in the definition of rapid eye movement sleep. Tonic electromyographic activity may be at a relatively low level, and so gains of around 20 μv cm^{-1} or higher are necessary. A minimum of high frequency filtering should be used, and time constants of 0.1 sec or faster are recommended to eliminate slower potenials from other sources. In the clinical assessment of sleep disorders recordings of respiratory rate and airflow, together with

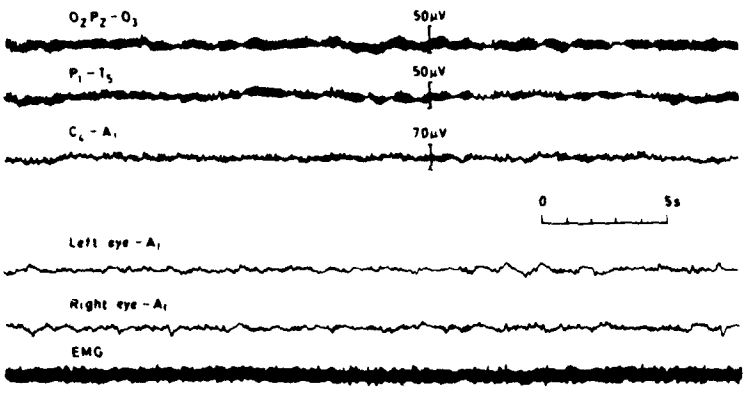

Fig.2 Awake activity in a subject with a dominant alpha rhythm seen most clearly in channels OzPz-03 and P1-T5. Electromyographic activity is sustained and of relatively high amplitude

oxymetry and myography of the anterior tibialis muscles, may also be needed.

STAGES OF SLEEP

Information from the electroencephalogram, electro-oculogram and electromyogram are used to define sleep stages. Records are read in epochs, usually of 30 seconds duration, and so with a paper speed of 10 mm sec^{-1} this corresponds to a page of 30 cm length. Each epoch is assigned to a single stage, although it is not considered in isolation. There are many occasions when the score depends on the features of the preceding and succeeding pages. When more than one stage is present, the one which takes up the greater portion is selected, and when more than half the tracing is obscured by muscle tension or amplifier blocking artefacts associated with movement of the subject the epoch is scored as movement time.

Wake Activity

The waking state (stage W) is characterised by alpha and/or a low voltage mixed frequency activity. Some subjects have virtually a continuous alpha record, while others may show little

or none. This stage is usually, but not necessarily, accompanied by a relatively high amplitude electromyogram together with blinks and eye movements (Fig.2).

Drowsy Sleep (Stage 1)

The change from a low voltage waking record to drowsy (stage 1) sleep is characterised by a general slowing of activity and by a decrease in the amount, amplitude and frequency of the alpha rhythm. When alpha activity together with low voltage activity amounts to less than 50% of the record and is replaced by relatively low voltage mixed frequency activity, the epoch is scored as stage 1 (Figures 3 and 4). The relatively low voltage, mixed frequency electroencephalogram characteristic of drowsy sleep has most activity in the 2 - 7 Hz range. The fast frequencies are of lower voltage than the 2 - 7 Hz activity. Stage 1 sleep tends to occur in the transition from wakefulness to sleep, or after body movements. During nocturnal sleep it is usually of short duration about 1 to 7 minutes. In the latter part of this stage 7 cps activity of high voltage (about 50 - 75 μv) may occur in irregularly spaced bursts, and vertex sharp waves may also appear. The amplitude of the vertex sharp wave is occasionally as high as 200 μv.

Absence of clearly defined K complexes and sleep spindles is essential to the definition of drowsy sleep. Traces of low voltage activity of 12 - 14 cps may begin to appear as stage 2 sleep approaches, but a rhythmic burst of at least 0.5 seconds duration is necessary for the record to be scored as stage 2 sleep. In stage 1 sleep, particularly after wakefulness, there are slow eye movements, each of several seconds duration, which are usually most prominent during the early part of the stage. Rapid eye movements are absent, and the amplitude of the electromyogram is usually lower than during relaxed wakefulness.

Sleep Onset

Stage 2 sleep is indicated when spindles and K complexes are present and when there is insufficient high amplitude, slow activity to indicate slow wave sleep. The first appearance of spindles and/or K complexes signals the onset of sleep. A sleep spindle must last for at least 0.5 seconds and should consist of at least 6 to 7 distinct waves of 12–14 Hz. K complexes are wave-

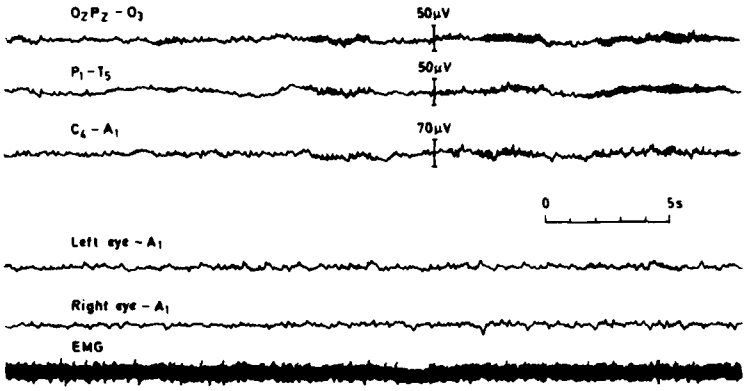

Fig.3 This recording illustrates the transition from awake to drowsy sleep (stage 1). Alpha activity decreases and is replaced by the relatively low voltage, mixed frequency activity typical of drowsy sleep. Electromyographic activity is maintained

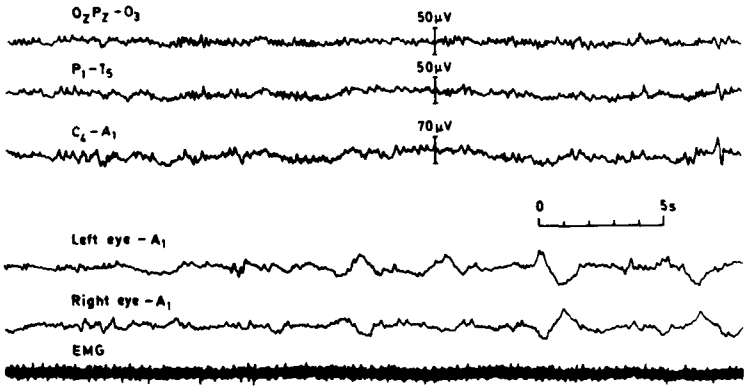

Fig.4 Drowsy sleep (stage 1). The electroencephalogram consists of relatively low voltage, mixed frequency activity. Slow eye movements can be seen in the electro-oculogram

forms which have a well defined negative sharp wave followed immediately by a positive component. The total duration exceeds 0.5 sec and waves of 12–14 cps may or may not constitute a part of the complex. K complexes can occur as a response to sudden stimuli, but they also appear frequently in the absence of any obvious stimulus (Fig.5).

Slow Wave Sleep

A record in which at least 20%, but not more than 50%, of the epoch consists of waves of 2 cps or slower (delta waves) with amplitudes greater than 75 μv from peak to peak (the difference between the most negative and positive points of the wave) is scored as stage 3. Wave by wave measurements are only necessary for epochs with borderline amounts of high amplitude, slow wave activity, i.e., around 20 and 50%. Sleep spindles may or may not be present in stage 3 (Fig.6). When more than 50% of the epoch consists of waves of 2 cps or slower with amplitudes greater than 75 μv from peak-to-peak the epoch is scored as stage 4. Although only slightly more than half of an epoch may contain high amplitude slow waves, most stage 4 epochs have the appearance of being completely dominated by this activity. Intervals of lower amplitude, faster activity rarely persist for more than a few seconds in this stage, though they are more prominent in stage 3 sleep. Sleep spindles may or may not be present in stage 4 (Fig.7).

Rapid Eye Movement Sleep

The appearance of relatively low voltage, mixed frequency activity together with episodic rapid eye movements indicates rapid eye movement (REM) sleep. The electroencephalogram has some resemblance to drowsy sleep, except that vertex sharp waves are not present. So-called "saw tooth" waves appear frequently, but not always, in vertex and frontal regions in conjunction with bursts of rapid eye movement activity. Alpha activity may be more prominent than during drowsy sleep, although the frequency is generally 1 to 2 cps slower than during wakefulness. As with stage 1, there are no sleep spindles or K complexes. Rapid eye movement sleep should not be scored when electromyographic activity is elevated. During rapid eye movement sleep the amplitude of the electromyogram is not higher than the level during the preceding sleep stages. Indeed it

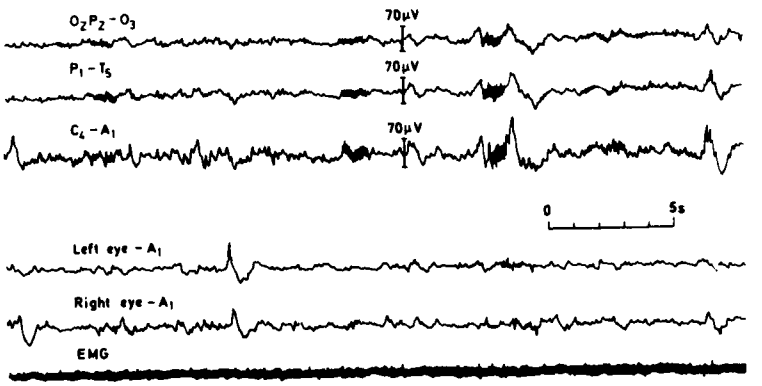

Fig.5 Stage 2 sleep (sleep onset). Stage 2 is characterised by the appearance of spindles and/or K complexes

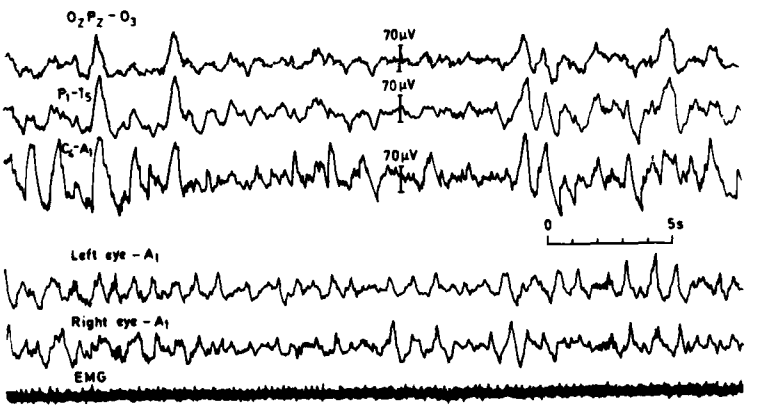

Fig.6 Slow wave sleep – Stage 3. This stage is defined by the presence of slow wave activity which occupies at least 20%, but not more than 50%, of the duration of the epoch

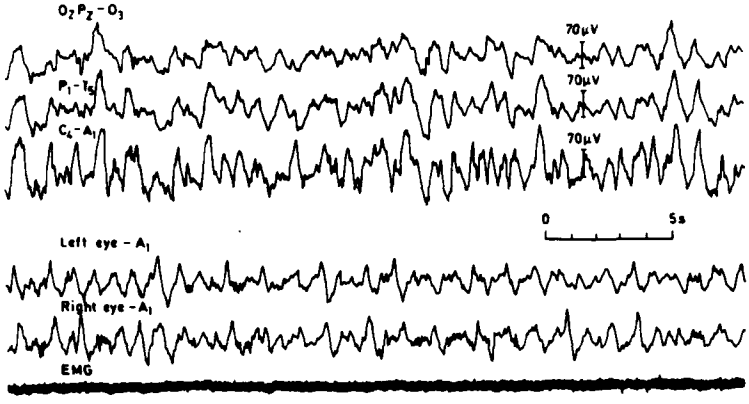

Fig.7 Slow wave sleep – Stage 4. This stage is defined by the presence of slow wave activity which occupies more than 50% of the duration of the epoch

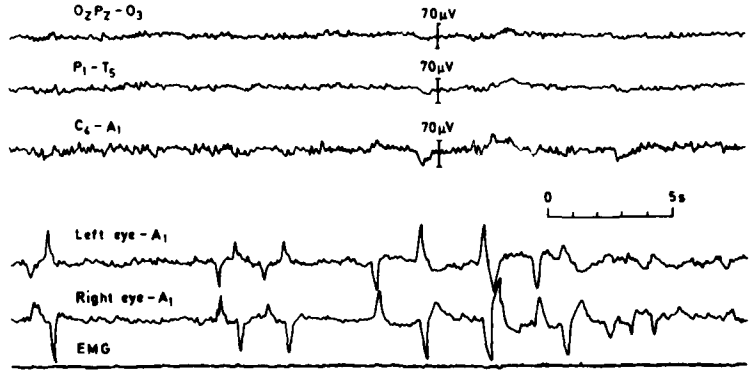

Fig.8 Rapid eye movement (rem) sleep. There is low voltage mixed frequency activity with episodic eye movements. Electromyographic activity is at its lowest level

almost always reaches its lowest levels during this stage of sleep (Fig.8).

THE SLEEP CYCLE

In general, the healthy young adult passes from waking into non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4) and about 70–90 minutes elapses before the appearance of the first period of REM activity, and this duration is often referred to as the latency to the first REM sleep period. The normal sequence is: waking, stage 1, stage 2, stage 3, stage 4, stage 3, and then stage 2. At this point the first period of rapid eye movement sleep occurs, and is followed by further non-REM stages (stages 2, 3, 4, 3, and 2) and then a further REM episode. The interval from the beginning of one REM period to the beginning of the next has a duration of about 90 minutes, but it may vary between 70 and 120 minutes. The mean duration of REM cycles changes during the night, with different patterns of change in different age groups.

As the night proceeds the content of the sleep cycle alters. Excluding the first cycle of the night, subsequent cycles have progressively decreasing amounts of slow wave sleep. The amount of slow wave sleep in the first cycle is age dependent, decreasing with advancing years. The REM episode in the first cycle is shorter than those in subsequent cycles, except in the elderly in whom it becomes progressively longer. In general, there is more slow wave sleep early in the night and REM sleep increases as the night progresses. An example of the night time sleep pattern in a young adult is shown in the hypnogram (Fig.9). Typical percentage for the whole night in the young adult are: 50% stage 2, 25% REM, 10% stage 3, 10% stage 4, and 5% stage 1.

Sleep Stages and Age

Total sleep time and the total nightly amounts of the various stages of sleep are age dependent. Total sleep time is longest in infancy, shortens in childhood and then remains relatively stable. The number of awakenings may increase with age. Rapid eye movement sleep duration is greatest in infancy and childhood, remains constant during adulthood, and decreases in old age. Stage 4 sleep duration is also highest in infancy and declines with

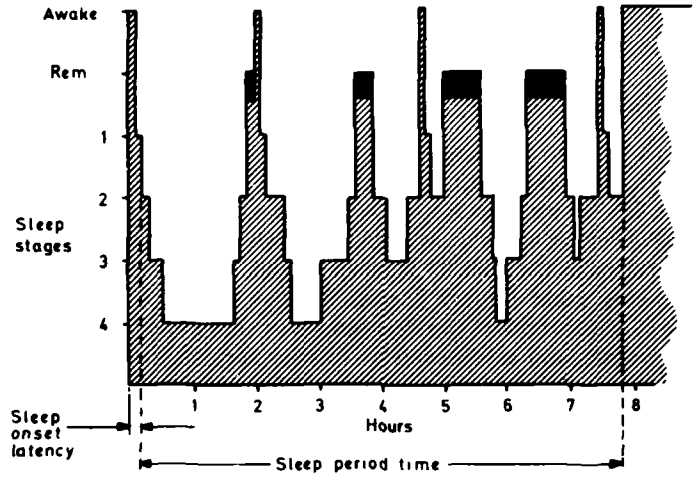

Fig.9 Hypnogram of a young healthy adult which illustrates the sleep stage transitions throughout the night

age. Though women may not be different from men in sleep duration during their twenties, they tend to have a consistently longer sleep time than men over the span of life. The number of awakenings is considerably higher for men than for women, and this difference continues until the seventies. The young adult sleep pattern is maintained somewhat longer in women.

NEUROENDOCRINOLOGY

In recent years there has been interest in the endocrinological correlates of sleep, as the secretion of many hormones is related to sleep and wakefulness, the sleep cycle itself or to specific electroencephalographic activity. With some hormones the relationship also varies with age. Circadian rhythmicity is also important, as well as the influence of the light-dark cycle and the episodic secretion of other hormones. Indeed sleep related secretion accounts for only part of the fluctuations in plasma levels.

Growth Hormone

In most subjects the peak plasma level of growth hormone is

seen during the first 90 minutes of sleep and the secretion lasts from 1.5 to 3.5 hours. When sleep onset is delayed, the plasma peak of growth hormone is also delayed, and when subjects are awakened for 2–3 hours and sleep is resumed, there is another peak. Smaller peaks occur throughout the night, and these tend to be related to slow wave sleep as two-fifths of the peaks are observed during these stages, whereas slow wave sleep occupies only about 15–20% of total sleep time. The pattern of growth hormone secretion is not related to plasma levels of glucose, insulin or cortisol.

The 24-hour pattern of growth hormone secretion varies with age. In the first few weeks of life, growth hormone levels do not vary between sleep and wakefulness, but after the third week of life waking values decrease considerably. Children secrete most growth hormone during sleep and little when awake, and during adolescence, both sleep related and day time secretion are greatly increased. There may well be some truth in the saying that children need sleep to grow. In young adults sleep related secretion is somewhat less than in adolescence, and in the elderly it is greatly decreased and this change may be related to the reduced amounts of slow wave sleep.

The secretion of growth hormone does not have an independent circadian rhythm, because after inversion of the sleep-waking cycle the pattern of secretion is also reversed. Since the percentage of slow wave sleep in the first 2 hours of sleep is normally high, it is possible that the plasma peak of growth hormone is related to sleep onset or to early sleep, and not to slow wave sleep *per se*. However, secretion is higher in afternoon naps when there is more slow wave sleep than in morning naps. It would therefore appear that growth hormone secretion is not specifically associated with sleep onset, but rather to slow wave sleep, and that it is related, not to duration, but to the onset of slow wave sleep. This may explain why there is no relationship between total amounts of slow wave sleep in the first four hours of sleep and the amount of growth hormone secreted, and why secretion remains normal even when the duration of slow wave sleep is reduced as with ingestion of some benzodiazepines such as flurazepam.

Total 24-hour secretion of growth hormone remains similar even when the pattern and times of sleep are drastically altered, and although the patterns of secretion differ greatly between

individuals, the individual pattern is relatively constant. In the Arctic with extremes of daylight and darkness, sleep related growth hormone secretion is similar during all four seasons.

Pituitary-Adrenal Axis

Blood cortisol levels are lowest in the early hours of sleep and highest in the early morning hours. Adrenocorticotrophic hormone (ACTH) secretion is lowest in the few hours before and after sleep onset, it increases after three to five hours of sleep and reaches its maximum just before awakening. Individual episodes of ACTH secretion tend to occur about 10 minutes before an episode of cortisol secretion. The pattern of ACTH and corticosteroid secretion is much less closely tied to the sleep-wake cycle than that of growth hormone. Circadian rhythms of urinary 17-hydroxycorticosteroid persist during sleep deprivation, and lengthening or shortening of sleep time has no effect on the diurnal plasma cortisol cycle. The cortisol cycle adjusts to a 19- or 33-hour sleep-waking cycle, or to inversion of the 24-hour cycle within 1–2 weeks. With subjects on 3-hour sleep-waking cycles (i.e. 1 hour's sleep followed by 2 hours' waking for periods of 10 days), the circadian rhythm of cortisol persists, though there is an ultradian rhythm with plasma cortisol levels lowest during sleep periods and highest in the first hour after waking. These phenomena are associated with sleep and not with the light-dark cycle.

It is difficult to be certain that any relationship exists between cortisol secretion and specific sleep stages, and this is in part due to its relatively long half-life of over an hour, which makes association with specific electrical patterns difficult. Since maximum plasma cortisol levels are normally reached after several hours of sleep, a relationship with REM sleep which is highest at that time has been suggested, and most peaks occur in or around REM episodes. Rapid eye movement sleep and cortisol secretion can, however, be dissociated, as in sleep inversion.

Prolactin

There is an initial peak in prolactin secretion between an hour and an hour and a half after sleep onset, with subsequent peaks reaching maximum levels between 7 and 8 a.m. During

the hour after wakening the levels begin to fall, reaching a minimum between 10 a.m. and noon. When the hours of sleep are modified, there is an immediate shift. In this sense prolactin secretion resembles that of growth hormone rather than ACTH, although it seems to have some stability as a circadian rhythm in addition to its relationship to sleep. However, unlike growth hormone, prolactin secretion does not seem to be related to a specific sleep stage.

Thyroid-stimulating Hormone

A general temporal relation of thyroid stimulating hormone secretion to sleep exists although the initial rise may occur in the hours immediately before nocturnal sleep and levels tend to fall during sleep. If sleep is delayed, thyroid-stimulating hormone levels climb for longer and this implies that sleep initiates the fall in plasma level. However sleep reversal studies have suggested that there is also an endogenous component.

Anti-diuretic Hormone

It is well established that urine output decreases at night, during which about one-third of the 24 hour volume is excreted. Anti-diuretic hormone secretion, like that of the anterior pituitary hormones, is pulsatile, but there appears to be no relationship to sleep stages.

CHAPTER 3

CIRCADIAN RHYTHMS

Biological processes may vary with respect to time in a periodic and regular manner, and such rhythms are present throughout nature from nucleated unicellular organisms to man. In man they involve the entire organism, as well as systems, organs and tissues, and they influence both his physiological and psychological activity. They are genetic in origin, and persist in the absence of time clues and cues, though they are modulated by variations in the environment. These regular cyclical changes can be represented by a sinusoidal curve (Fig.10), and are described by four measures.

Period. The time between two recurring and similar points in a rhythm, or the time to complete one cycle. A period can be as short as a micro-second, or as long as a year (circannual rhythm). In man rhythms with a period of about 24 hours (circadian) are of particular interest.

Acrophase. The point during the period at which the maximum value is expected to occur. It is the peak of the cosine

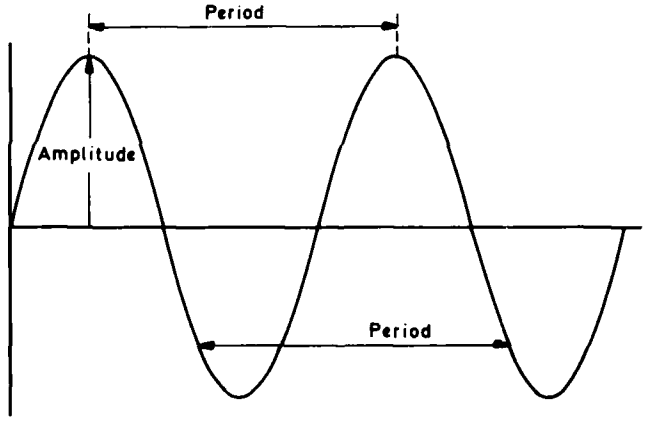

Fig10 Measures used to define a circadian rhythm

function which most accurately fits data collected as a function of time. For example, it could be the time of day when body temperature is highest. Since the acrophase is located on a time-scale, a phase reference is usually given, and this is usually mid-night for a circadian rhythm.

Amplitude. The magnitude of the variation of the rhythm. It is sometimes given as the peak-to-trough value, and sometimes as the "half amplitude" or mean-to-trough or peak. The term range of oscillation may be used when a rhythm is not symmetrical.

Mesor. The average of all the values collected at equal intervals during a complete cycle. It is sometimes called the rhythm adjusted mean.

ORIGIN OF RHYTHMS

Daily rhythms of sleep and wakefulness, urine production and body temperature are well recognised, but the question arises whether they originate from within the organism or are the result of some exogenous influence. With temperature the higher value observed in the day and the fall at night may merely relate to the activity of the individual, but temperature and many other diurnal rhythms persist in the absence of external influences and are, therefore, believed to be endogenous. They are free running, self-sustaining oscillations with a periodicity between 21 and 26 hours, and it is for this reason that they are known as circadian rhythms. They are brought into phase by rhythmic environmental synchronisers with an exact 24 h period dependent on the rotation of the earth. Synchronisers which are also known as cues, entraining agents or zeitgebers include light and temperature and their often dependent functions such as work schedules.

Endogenous circadian rhythms have been established for at least fifty physiological, biochemical and psychological variables, and their times of maxima and minima, as well as amplitude, differ. These rhythms may be influenced by at least forty variations in the environment, and in any particular situation there may be single or multiple cues. To determine whether a rhythm is endogenous in origin it is necessary to remove all cues to time. This is particularly difficult with man who is subjected to the alternation of light and darkness with an almost constant

cycle length, and who has developed a pattern of behaviour with alternating periods of rest and activity and regular meals. This social organisation also influences those without sight as well as night and shiftworkers whose activity differs from that of the usually accepted pattern of work and rest.

Under constant conditions such as those achieved in bunkers and isolation units, biological rhythms oscillate with a spontaneous period length which differs from 24 hours. Furthermore, the frequency or period of different systems such as body temperature and activity, may vary – a phenomenon known as "internal desynchronisation". The persistence of rhythms under constant conditions as well as internal desynchronisation is evidence that circadian rhythms are endogenous in origin, and possibly controlled by more than one "internal clock".

Circadian patterns of performance and work output in field studies are similar to those observed in the laboratory, but the range of oscillation is much greater and may be as high as 100% of the 24-hour mean. A secondary trough in performance is often present just after noon. This so-called "post-lunch dip" persists even when the subject misses the meal usually eaten at this time, and unlike the fall in performance at night it is not associated with a decrease in body temperature.

PHYSIOLOGICAL RHYTHMS

In addition to temperature, excretory and activity rhythms, there are circadian rhythms of the electrical activity of the brain, cell division, and serum content of specific substances, examples of some variables and their acrophases in man are given in Figure 11, while circadian rhythms of temperature, 17-OHCS, adrenaline and noradrenaline are illustrated in Figure 12. By the first week of life some rhythmic activity is apparent, though the rhythms of premature babies develop later than those of full term infants. Skin resistance peaks in the late morning and there is a sleep-wakefulness pattern with a period around 24.4 hours. Infants exposed to a 4 hourly regular routine tend to develop the sleep-wakefulness rhythm sooner than those reared alone or fed on demand. It has been proposed that organs which are well developed at birth such as the skin show a circadian rhythmicity earlier than those which take longer to mature. In this way functions within the same organ may develop rhythmicity at

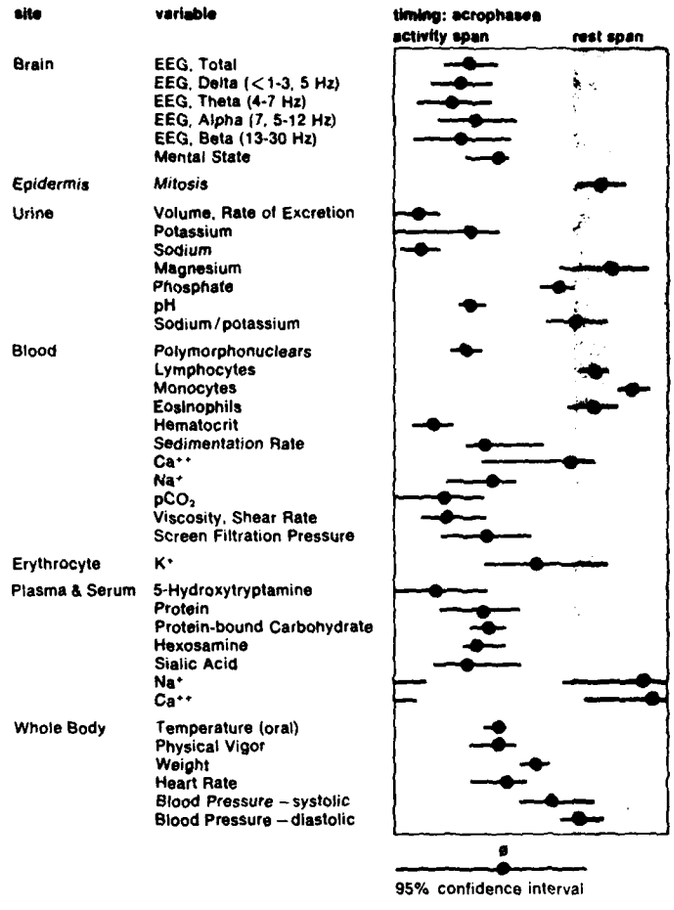

Fig.11 Circadian acrophases for various physiological functions in healthy man
Reproduced from Reinberg, A. (1974). Chronobiology: Basic Definitions. In: The Fourth Dimension of Medicine: A Symposium on the Critical Implications of Chronobiology. By kind permission of the Upjohn Company, Kalamazoo, Michigan

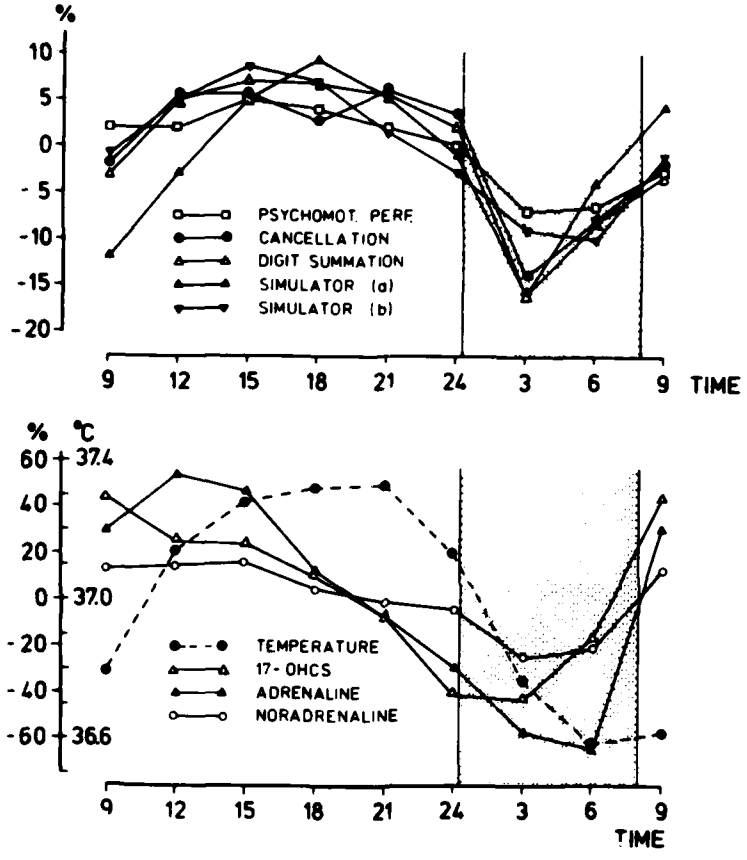

Fig.12 Circadian rhythms of some physiological and psychological functions in healthy man
Reproduced from Klein, K.E. and Wegmann, H.M. (1980). AGARDograph No.247 Advisory Group for Aerospace Research and Development, Neuilly-sur-Seine

different times. Water excretion which depends principally on glomerular filtration shows a circadian rhythm before electrolyte excretion which is dependent on tubular function.

PERFORMANCE

On most tasks performance rises during the day to a peak or plateau between 1200 and 2100 hours and falls to a minimum usually between 0300 and 0600 hours. The pattern is similar to that of body temperature and has been shown for a large number of skills including addition, cancelling symbols, vigilance, card sorting and choice reaction as well as performance on an aircraft (F104) simulator, some of these patterns are illustrated in Figure 12. However, scores at tests involving memory tend to peak in the morning and fall steadily during the day, and the correlation between performance and temperature changes from positive to negative as the memory load of a task is increased. Memory functions not only show differences in phase but also lower ranges of oscillation. A task with a high memory load tends to adapt faster than other tests to simulated night work and to the time shifts inherent in transmeridian flight, and these results have been used to suggest that a negative correlation may exist between rhythm amplitude and speed of adjustment.

Many factors may modify performance rhythms (Fig.13). If subjects stay awake the phase of the rhythm tends to drift toward later hours and during the first night awake the range of oscillation is smaller. As sleep deprivation continues it may increase again, though the 24 hour mean of performance will fall. The effects of sleep deprivation are augmented by uncertainty in the task and in the response required. There have also been attempts to link behaviour and personality with rhythmicity in performance. Those who perform well in the evening tend to have later maxima and minima of performance than those who perform well in the morning and their spontaneous period in the free running state is longer. However, correlations with extroversion and introversion scales, though described, may not be strong. Further, practice and extra effort will reduce the amplitude of performance rhythms, while workload and the stress imposed by the task, will increase amplitude. The range of oscillation tends to be low for simple tasks with highly motivated subjects, and high for complex tasks with subjects with poor motivation.

Performance over long periods of time may also be influenced by an interaction with the circadian system. Performance degradation may depend on the stage of the

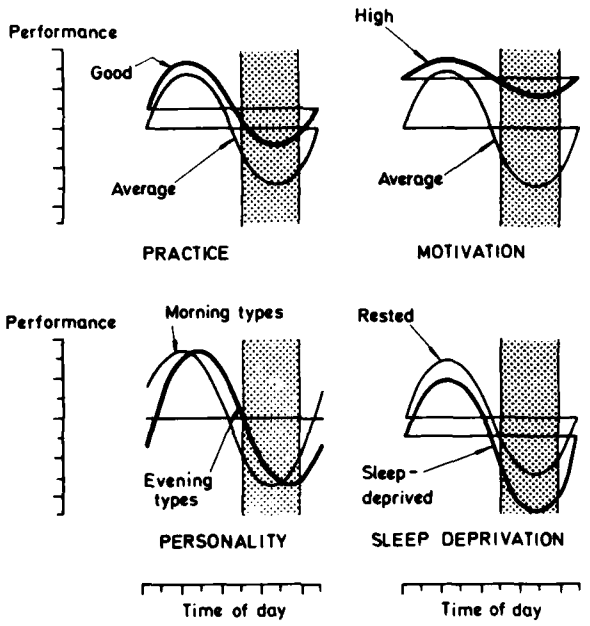

Fig.13 Schematic representation of the modification of circadian behavioural rhythms
Adapted from Klein, K.E., Wegmann, H.-M., Athanassenas, G., Hohlweck, H. and Kuklinski, P. (1976). Air Operations and Circadian Performance Rhythms. Aviat. Space Environ. Med., 47, 221-230

circadian cycle with which it coincides. When prolonged duty begins at noon, the maximum performance decrement is between 10 and 15%, while when the same work starts at midnight, the maximum decrease is as much as 35%. It would appear that the increasing levels of arousal during the day partly compensate for the effects of prolonged work whereas the natural decrease in alertness at night may add to the problem. Auditory vigilance as well as tests related to instrument flying in simulated transport flights show this pattern. The inclusion of a sleep period during long periods of work is of benefit. When work periods of four hours duration starting at 2000 h and 0400 h are separated by a period of sleep, the fall in performance at the circadian trough is reduced.

PHYSICAL ACTIVITY

Physical activity may also modify performance and its circadian pattern. Light to moderate exercise improves mental performance whereas heavy work decreases performance, and the effect is dependent on time of day as well as the task being studied. Studies on visuo-motor coordination have shown improvements in the morning and afternoon after a period of work but this is not so in the late evening and early night. On the other hand the same exercise tends to impair tests which involves memory at any time of the day. Heart rates at rest also show a circadian variation of about 8–12% with the minima occurring at night, though the difference decreases with increasing physical workload and is near zero at maximum effort. The usual prediction of aerobic work capacity from heart rate at submaximal exercise does not therefore hold when the circadian rhythmicity of physical performance is considered. At night the oxygen consumption in relation to work output is lower at maximum effort, and work outputs equivalent to those during the day can only be produced with a higher physiological cost with about 8–10% extra oxygen uptake.

CIRCADIAN RHYTHM DISTURBANCE

In man, the clock hour and day time-related social activities, such as meals, work and rest – in particular the beginning and end of sleep – appear to be more important in entraining rhythms than the light-dark cycle of the environment. It is the inability to adapt to a sudden shift of these external synchronisers which causes a transitory desynchronisation of the circadian rhythmicity of the individual with that of the environment. Such a dissociation of circadian rhythms may be brought about in many ways. Abnormal time routines may be imposed, isolation from time cues may be effected, and rapid phase shifting across a number of time zones follows transmeridian flights. The change can involve one, several or all of the measures which define a circadian rhythm.

Subjects can be almost perfectly isolated from natural time cues in deep caves, underground bunkers and isolation chambers. Under such constant conditions the circadian system will free run and most subjects will show a spontaneous period close to 25 hours. In the free running situation most rhythms

remain synchronised with each other, but in some individuals the period length of activity rhythms may vary from 30 to 40 hours whereas the temperature rhythm maintains a period around 25 hours. This is called internal desynchronisation. Free running circadian rhythms seen under constant conditions can be modified by external stimuli, which act as artificial synchronisers. However there is a limit to the period length which can be superimposed and physical cues are probably less effective than those which involve social interactions.

In the world outside bunkers and isolation chambers, conflict of the circadian rhythm with that of the environment can also arise. The zeitgebers in the environment may change their period length, become weakened or disappear completely. This occurs in submarine and space operations, but in principle is also present in other situations of partial or total removal from external periodic inputs, such as living in the Arctic, or in the confinement of a shelter. When rest and activity patterns are out of phase with the environmental synchronisers, conflict may also arise and this condition is found in shiftworkers particularly when night work is undertaken. Finally after transmeridian flight there is a phase shift in the environmental timing system, and this change may be repeated often in aircrew involved in world-wide operations.

Circadian rhythmicity may also be disturbed in disease. The rhythmic activity of the electroencephalogram and that of plasma 17-OHCS may be desynchronised in epilepsy, circadian oscillations of several functions may be increased in diabetes and the amplitude of many rhythms may be decreased in psychoses. The peak time for attacks of asthma and myocardial insufficiency is around 0400 h. Sensitivity to some drugs also varies with time of day. Cardiac patients are more sensitive to diuretics in the evening than in the morning and to digitalis at night than during the day. The response of diabetics to insulin is maximum around 0400 h, and the maximum rate of alcohol metabolism occurs between 1400 h and midnight.

CHAPTER 4

SHIFTWORK

Shiftwork is required for a variety of reasons, and economic considerations have played an important part in the increase of this activity. When we work by day and rest at night the circadian variations in our physiological and psychological functions are in harmony with this routine, but in shiftworkers rest and activity patterns are out of phase with the environmental synchronisers. A single night shift does not change the circadian rhythm of body temperature. Consecutive night work for at least seven days is required to shift the time of minimum temperature to a point within the new sleeping period, though it is not clear whether other physiological functions re-entrain at the same rate.

The extent and significance of dysynchrony in shiftworkers depends on the individual as well as the work-rest pattern. Even though some shift systems do not involve nightwork, early morning shifts (0600–1400 h) may cause difficulty, whereas with nightwork some may choose it permanently and others may prefer rotation between day and night. Some shift systems include weekends and in these abnormal rest and activity patterns may be a permanent feature. Even so disturbed sleep is one of the major consequences of shiftwork. The night worker is forced to rest during the day when environmental factors do not favour sleep. There is the obvious increase in light and noise levels, and these changes may be more easily appreciated during the light sleep of the day. There are also higher ambient temperatures and social influences which may disturb even the most tired morning sleeper. Indeed in a group of workers who slept nearly 8 hours at night, only about 5½ hours sleep was obtained during the day. With morning sleepers the later they retire the less they may sleep.

SLEEP DISTURBANCE

Some examples of sleep durations on different shifts are given in Figure 14. It can be seen that sleep length related to morning shiftwork is close to that obtained by those on a night shift, and this would suggest that it may not be the night shift

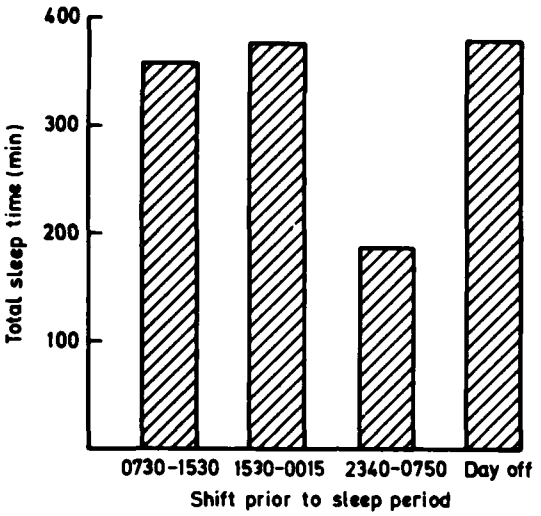

Fig.14 Average total sleep time (min) for four shiftworkers after morning, afternoon and night shifts, and after off-duty periods. Sleep during the day after the night shift is of shorter duration than that under any of the night time conditions

alone which causes difficulties. Subjectively, shiftworkers rate differentially the quality of sleep at various times. In particular, that after the night shift is rated worse than that after other shifts. Sleep before an early morning shift will be curtailed because of the schedule, and this may have an adverse effect on well-being, whereas the end of a sleep period after a night shift-work is more determined by the individual.

It is not only the length of sleep that is important, but also its "quality". In shiftworkers there are no differences in sleep onset but drowsy sleep tends to be increased and stage 2 sleep reduced. Rapid eye movement sleep may occur immediately after falling asleep during the day, although the durations of rapid eye movement and slow wave sleep do not appear to be changed. The temperature cycle may influence the inability to maintain daytime sleep. There is a tendency to wake up just before the peak in body temperature, and studies in isolated environments have suggested that when body temperature is low, the

probability that one will sleep is high and *vice versa*. The duration of sleep may therefore depend on the position of the sleep period within the temperature cycle.

AGE AND SOCIAL FACTORS

Older people may have difficulty in adapting to shiftwork. Total sleep requirement decreases although more naps may be taken. Furthermore, those over 50 years of age are generally less flexible, both physiologically and socially than young people. Indeed a major predictor of sleep length and sleep quality in those who work at night is the age of the worker – increasing age being associated with more problems. On the other hand this relation may be reversed for early morning work, and so a general difficulty in shift working is not related to aging. Indeed, this suggests that age related changes in circadian rhythms may be involved. "Morningness" may increase with age with earlier peaks in temperature and activity rhythms. It is also possible that internal desynchronisation of the circadian system becomes more likely with increasing age, making the individual more susceptible to disturbances of the sleep-wakefulness cycle. In experienced workers problems with the night shift may appear around 45 years of age.

Although the physiological disturbances associated with shiftwork have been studied in detail, social difficulties are probably the more important for the shiftworkers themselves. It may be possible to plan shift systems which minimise physiological disturbances, but these may not be acceptable as they may involve undue disruption of family and social life. Indeed in the design of schedules, social needs as well as physiological considerations must be borne in mind.

SHIFTWORKING AND PERFORMANCE

Rhythms of body temperature and simple performance follow a similar pattern over a 24 hour period, with a minimum in the early morning hours. However, tasks requiring a higher level of cognitive abilities, such as short-term memory or logical reasoning, may have a pattern completely out of phase with that of temperature. Therefore when night work involves "simple tasks", performance during a night shift may be worse than during a day shift, whereas, this may not be the case for more

complex tasks. Efficiency tends to follow this pattern and during two weeks of consecutive night work gradually changes from a pronounced within shift decrement to a relatively constant level of performance. In general, memory loaded performance rhythms seem to adjust more quickly than others to changes in the sleep-wakefulness cycle.

However, considerable individual differences between subjects exist. Temperature and "simple" performance curves vary in phase and according to whether the individual is a morning type or an evening type as defined by questionnaires. This may have implications for selection. Further, some subjects are able to carry out shiftwork throughout their working lives without problem, whereas others suffer from fatigue and sleep disturbance as well as other symptoms such as gastrointestinal disorders after several years, or even after several months. At present it is not possible to forecast whether or not a subject is likely to tolerate shiftwork easily for many years. However, it has recently been suggested that a good tolerance to shiftwork is associated with large amplitude circadian rhythms and a slow adjustment to altered schedules. This does not imply that the natural circadian amplitudes differ between tolerant and non-tolerant shiftworkers indeed under normal conditions the amplitudes of the poor shiftworker may be within the usually accepted range. It would appear that it is the response of the circadian system to altered work patterns which differs. If this is true, schedules that do not allow the subjects' temperature rhythm to adjust to a new "synchronisation" would appear to be preferable, and this would imply that a rapid rotation (change every 2--4 days) is a better choice than weekly rotation.

OPTIMAL SHIFT SYSTEMS

Although it is not possible to design a single system which is optimal for all shift workers and for all working conditions, certain criteria should be considered. Single are better than consecutive night shifts, as circadian rhythms are not significantly altered by working a single night. While it is true that working for more than seven nights allows re-entrainment, for social reasons most workers prefer a change of shift or rest days after no more than one week. Re-entrainment is therefore not normally possible. At least 24 hours of free time is desirable after each night's shift. Sleep disturbances and reduced sleep

duration are common complaints, and accumulated sleep deficit over several days should be avoided. To prevent sleep deprivation, a substantial recovery period is desirable. Similar problems may arise with early morning workers. In this case a 24 hour rest is also beneficial, though reorganisation of the shift system with later starting times would be an alternative solution.

The length of the shift should be related to the type of work. With light work the shift duration may be extended to 12 h, but it should not exceed 8 h, or even 6 h, when heavy physical expenditure or a high mental workload is involved. The cycle of the shift system should not be too long (i.e. 4 weeks is better than 40 weeks), and a regular system of rotation is preferable to an irregular one. Short cycles and regular systems make it easier for the worker and his family to arrange their social life. In the case of continued shiftwork, it is important to arrange as many free weekends as possible so that a reasonably normal social life is possible.

SELECTION

Because shiftwork cannot be sustained by about 20% of the working population, selection is important. It is not yet possible to give definite criteria, but shiftwork is contraindicated for some groups. New employees living alone, those under 25, and those over 50 years of age should be considered carefully, though experienced, well adapted individuals can in many cases remain in shiftwork beyond the age of 50. A history of digestive tract disorders may lead to problems which may be exacerbated by unusual times of meals or to increased caffeine and smoking which is common in nightworkers. Diabetics and patients with thyrotoxicosis may also find it difficult to ensure regular food and correct timing of medication and the incidence of fits in epileptics may be increased by sleep reduction.

CHAPTER 5

TRANSMERIDIAN FLIGHT

Transmeridian flights which involve displacements across latitudes produce rapid and often large time zone changes which desynchronise environmental and biological circadian rhythms (Fig.15). The displacement is also likely to lead to disturbed sleep. Subjectively most people complain of tiredness, loss of appetite and a general feeling of loss of well-being, while bodily functions such as sleep and wakefulness occur at unusual and often inconvenient times. Desynchronisation of the environmental and biological rhythms also affects psychological variables, and this may influence performance at certain times of the day. The need to synchronise rhythms to a new time zone may lead to difficulties for passengers and aircrew, though aircrew may be involved in repeated crossing of time zones over several days and their problems be much more complex. The adaptation of aircrew to complex schedules of work and rest is dealt with in Chapter 5.

POST-FLIGHT DESYNCHRONISATION

The nature of post-flight desynchronisation of circadian rhythms has been examined in several studies. After westbound flights the curve is displaced to the left and after eastward flight to the right. The amplitude may be altered and sometimes a rhythm will disappear. There are also changes in the 24 hour mean and at certain times of the day there may be lower values of some variables than pre-flight. Re-entrainment of rhythms to the new environment occurs gradually, and with body temperature may not begin before the onset of the first sleep in the new time zone. There may be differences in the shift of maxima and minima leading to distortions of the form of the original oscillation. After westward flight the maximum may shift earlier or further than the minimum, whereas the opposite may be true after eastward flights. Phase shifting is a specific consequence of the dysynchrony between the environment and biological rhythms, whereas other changes in the rhythms may be more related to the general stress of the flight.

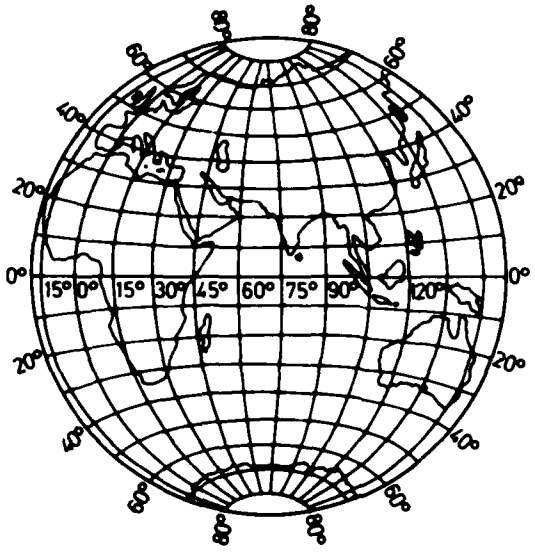

Fig.15 Globe with meridian intervals equivalent to one hour time difference or one time zone
Reproduced from Klein, K.E. and Wegmann, H.M. (1980)

In principle mental performance adapts in the same way as physiological rhythms. Psychomotor performance responds to a rapid phase shift in a similar manner to body temperature. Performance is impaired in the late afternoon and early night of the first day after crossings in a westerly direction, and in the morning and afternoon after travelling eastwards. Some reduction in 24-hour means of performance may occur after transmeridian flights, but the relative contribution of rhythm disruption and other factors such as fatigue is uncertain. Studies on performance after simulated time zone shifts indicate a direct effect of the disturbed time structure, although displacements of performance rhythms without alteration in the 24-hour mean suggest that a change in the overall level of performance is not an inevitable sequel of such travel. Early studies on performance involved simple tasks, but, more recently, tasks which may be more relevant to the skill and complex activity of present day air operations have been studied. After westard flights about 10

days may be required for performance to realign whereas after eastward flights 12 days may be needed.

Sleep disturbance after transmeridian flights may be seen as difficulties in falling sleep, spontaneous awakening during the night and early morning awakening. After a westward flight with 8 hours displacement, tiredness is likely to be experienced in the late afternoon, but when it is local time to sleep the individual may begin to feel awake. Electroencephalographic studies of sleep have shown that the circadian rhythm of rapid eye movement sleep with its usual morning peak takes a few days to adjust to a new time zone, and after westward flights when sleep is delayed rapid eye movement sleep occurs earlier in the sleep cycle than at home. Slow wave sleep does not appear to follow a circadian pattern, and is more related to the amount of prior wakefulness.

RE-ENTRAINMENT

In man social cues and timing of meals are important to the speed of re-entrainment. Indeed, their correct timing may accelerate the phase shift. Nevertheless, individuals differ in the ease and the speed of their adaptation. Using psychomotor performance rhythms as an indicator, resynchronisation times for the westward direction vary from between 1.7 and 6.0 days and for the eastbound direction from between 2.9 and 11.3 days. Indeed in some subjects, eastbound travel may require much longer times for complete readjustment. Circadian rhythms may also synchronise with the environment at different speeds, and this is true for psychological performance as well as physiological functions. However, it is not clear what causes dissociation. As far as performance is concerned it would appear that task complexity is important. A higher memory load adapts faster than simple performance tasks. It has also been observed that rhythms which are most persistent such as temperature, 17-OHCS and psychomotor performance may have the most pronounced amplitude whereas variables in which it is often difficult to establish a rhythm entrain quickly to new time zones (Table I).

SUMMARY

In summary the important changes in circadian rhythmicity

associated with transmeridian flight include the temporal displacement of the rhythm, changes in amplitude and in the 24-hour mean. As far as psychological function is concerned, this may lead to a relative lowering of efficiency at some parts of the day though with higher values at other times.

TABLE I

Shift Rates After Transmeridian Flights (minutes per day)

Function	*Westbound*		*Eastbound*	
Catecholamines (urinary)		135		90
Adrenaline	90		60	
Non-adrenaline	180		120	
Mental performance		93		57
Psychomotor performance	52		38	
Reaction time (vigilance)	150		74	
Heart rate		90		60
Body temperature		60		39
17-OHCS (urinary)		47		32

CHAPTER 6

AIR OPERATIONS AND IRREGULARITY OF WORK

Irregularity of work in air operations presents many problems in the management of aircrew. With short-haul routes services relate to the hours of business and commerce, and duty hours may extend on either side of the normally accepted times of work, while with long-haul operations duty may start at any time of the day or night, and crews have to cope with repeated time zone changes. Adequate sleep is important in the adaptation of aircrew to irregular work, and circadian rhythmicity may influence their effectiveness at certain times of the day.

LONG-HAUL OPERATIONS

Though sleep is of equal importance to aircrew involved in long-haul or short-haul routes, it has been the sleep of pilots operating world-wide east-west routes which has received most attention. The rest and activity of a pilot involved in long-haul routes is illustrated in Figures 16 and 17. It can be seen that, by the end of some duty periods, it may have been 16 hours since the end of the previous sleep period, and so there is a natural, if not urgent, desire to sleep. With a 24-hour off-duty period, a long sleep immediately after a flight would mean that the crew were not in the most rested state possible for the next duty; and so, to avoid undue sleepiness during duty after a 24-hour rest, crews often split their sleep into two parts. The need for sleep immediately before duty is created by restricting sleep immediately after the preceding flight. This leads to sleep periods of 3–4 hours during long-haul schedules (Fig.18).

During flights which extend wakefulness beyond 16 hours and flights which start during the early evening, naps of ½–1 hour duration are not uncommon, and they assist in the adaptation to new time zones, particularly on westward flights when the day is lengthened. The sleep patterns of long-haul crews contain many naps, but there are also long periods of sleep, and so the sleeps of the long-haul pilot range from ½ hour to ½ day in length (Figure 18). The sleep over any 24-hour period is also different in the long-haul pilot during flying duty when compared to non-flying duty (Fig.19).

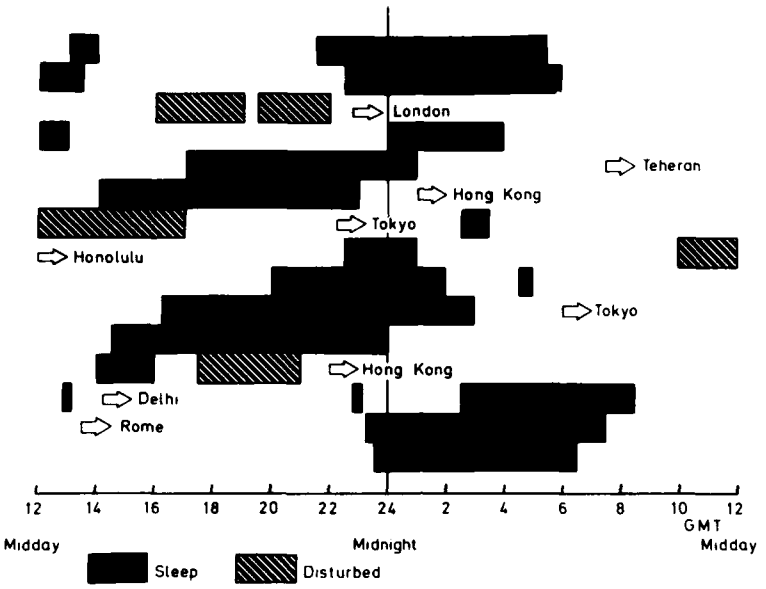

Fig.16 Sleep periods of an airline pilot operating a return flight from London to Honolulu via Hong Kong. The days in the schedule are read from the bottom line up, and each line is 24 hours with the extremes at midday. Onset of each duty period is indicated by an arrow, and periods of sleep which are considered to be disturbed are hatched

Sleep

In comparison with normal sleep patterns aircrew *en route* may have reduced sleep latency, particularly if prior wakefulness is long and stressful. This has also been observed during the first postflight night and after eastward time shifts. Later, the sleep latency may be prolonged. However, awakenings and transitions between sleep stages occur more often, and the increase in awake time may cause a reduction in total sleep time, especially if time in bed is limited by the schedule. Delay to the first REM period may be reduced, but the duration of REM sleep may be less. This change has been observed after westbound and eastbound flights and for the first postflight sleep

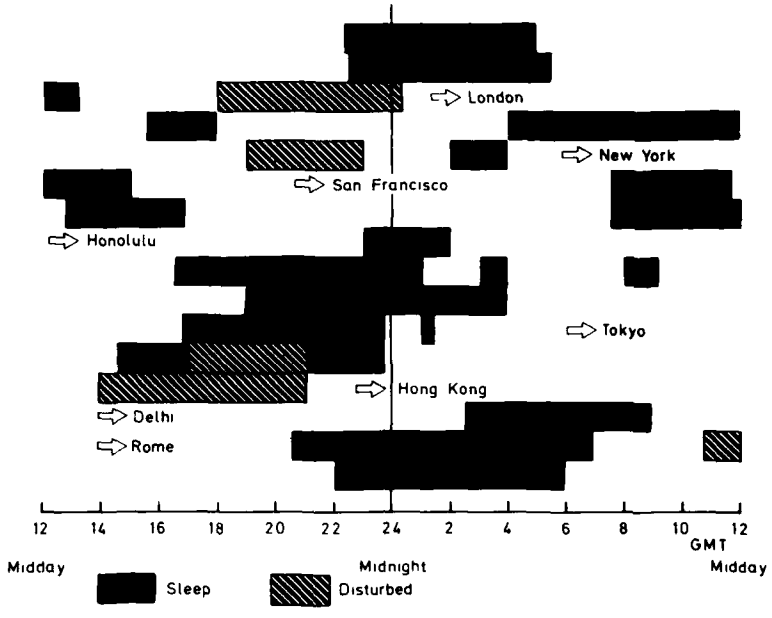

Fig.17 Sleep periods of an airline pilot operating a round-the-world flight from London via Hong Kong and San Francisco. The days in the schedule are read from the bottom line up, and each line is 24 hours with the extremes at midday. Onset of each duty period is indicated by an arrow and periods of sleep which were considered to be disturbed are hatched

period. Nevertheless sleep tends to adapt quickly to shifts of environmental time cues, and in general it is complete within a few days, if the individual remains in the new time zone.

Though little is known about the physiology of sleep in aircrew *en route*, it is clear that naps, sleeps of 3 -4 hours and long periods are all attempts to adapt to irregular duty hours and time zone changes, and to ensure adequate rest before the next duty period. From experimental work in the laboratory it would be reasonable to assume that the natural requirements for sleep may be preserved even though the timing and duration of sleep

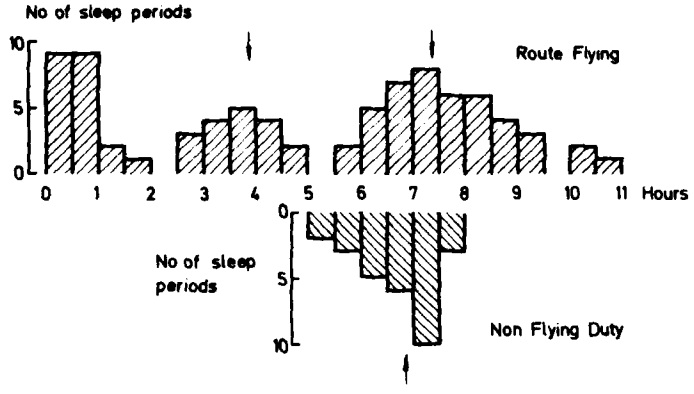

Fig.18 Duration (hours) of sleep periods in a pilot during world-wide, east-west operations

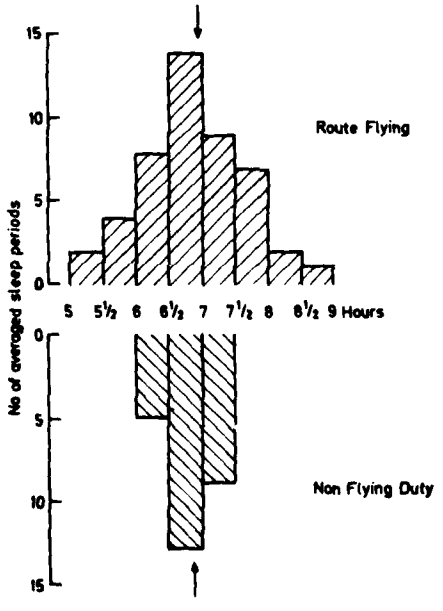

Fig.19 Histogram for assessed length of sleep periods during route flying and during non-flying duty in an airline pilot

periods are changed. The essential problem for aircrew is disturbance of their normal sleep pattern, and the personal modification of the desire to sleep plays an important part in the adaptation to irregular work. These considerations apply to disturbed sleep without undue sleep loss. A more serious situation arises when disturbed sleep merges into a rest and activity pattern which involves sleep loss over a 24-hour period preceding the end of duty or the accumulation of loss of sleep.

SHORT-HAUL OPERATIONS

There is less information available on the rest and activity patterns of aircrew involved in short-haul operations. Services between international centres of commerce relate to normal working hours, and so aircrew duty encroaches on the normally accepted rest period. In short-haul operations with acceptable schedules, sleep periods are likely to be shortened. The mean duration of sleeps over several months is similar to that observed in normal day-to-day activities (7.6 hours) though the range of sleep period lengths is much greater. It varies from less than 5 hours to more than 9 hours, and this would appear to be the adaptation of the short-haul pilot to duty hours which encroach on early morning and perhaps late evening sleep. Naps are not a feature of the adaptation of the short-haul pilot – prolongation of some sleep periods is the essential compensation, and such modifications may involve many months of the year.

CIRCADIAN DISTURBANCE

Though it is not difficult to appreciate the importance of disturbed sleep brought about by irregular activity, it is, perhaps, more difficult to be certain of the importance of disturbance in the rhythmic nature of man. Regular variations in certain functions are related to the alternation of day and night, and this activity is important when man is required to adapt to unfamiliar patterns of activity. Endogenous rhythmic activity tends to place certain forms of behaviour in their proper relation to the environment. Man can be less efficient at night, when he is not required to function at optimum levels of performance, and so performance exhibits a circadian rhythm. Circadian rhythms may be important in air operations: the question arises whether rhythmicity of performance such as vigilance may play a part in air accidents. When activity is imposed on time usually reserved

for sleep, there may be reduced performance, and the stress of the flight may add to the deterioration. Further, flight stress may reduce any circadian elevation in performance. With this information it is possible to suggest the most likely times of minimal performance for relatively simple transmeridian flights, and avoid landings when the pilot's performance would be at a particularly low level. However, in aircrew involved in world-wide operations over many days it would not be possible to predict so easily the times of reduced performance.

DUTY HOURS

It is evident that the irregular work of air operations leads to disturbances of sleep and of the circadian activity of man. It is difficult, other than by avoiding night landings in aircrew with relatively simple transmeridian schedules, to avoid the possible hazard associated with falling levels of performance, but duty hours should be arranged to ensure that aircrew can create an acceptable sleep pattern. There is a cumulative effect of irregular work, disturbed sleep and circadian desynchronisation, and a critical factor in determining acceptable work is probably the total duty hours expected over a number of days. Perhaps the duration of rest periods after flights should be more related to the preceding workload, and so fixed minimum rest periods of limited duration may no longer be acceptable in the design of aircrew schedules. A logarithmic relationship between total duty hours and number of operating days which takes account of this cumulative effect (Fig.20) has been proposed for aircrew involved in multiple time zone crossings rather than a simple return transmeridian flight. With this relationship, it is possible to design schedules least likely to lead to sleep difficulties (Tables II and III).

It can be seen that a small increase in duty hours may convert an acceptable to an unacceptable schedule, and so a small reduction in the overall number of duty hours is likely to be beneficial. Such a modification may provide an additional period of sleep within a schedule of a week or two or provide greater flexibility in the choice of time to sleep during a longer rest period. It is hardly possible to create ideal schedules among the complexities of present-day operations, but with care reasonably satisfactory ones can be found. Planning should also include the facility to hasten an operation, and to cope with the extra workload which minor changes in crew availability create.

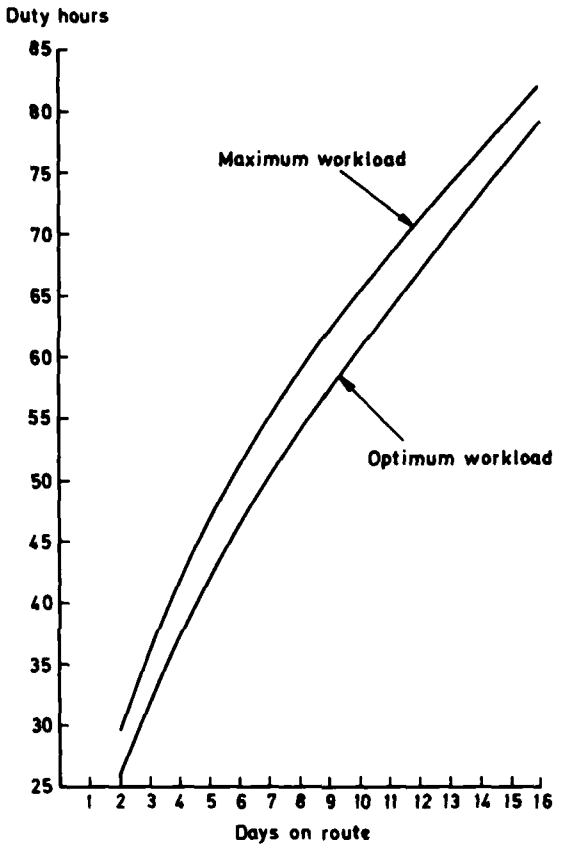

Fig.20 Duty hours for days *en route* suggesting workload (duty hours) compatible with an acceptable sleep pattern (optimum workload) and duty hours unlikely to be compatible with an acceptable sleep pattern (above maximum workload). The curves are logarithmic

MANAGEMENT OF AIRCREW

To manage aircrew who have to cope with irregular rest and activity is not a simple matter, though the key to the problem is the appraisal of duty hours. Long-haul operations incompatible

with an acceptable sleep pattern and busy short-haul schedules over many months could prejudice the safety of air operations, and so duty hours are of legitimate interest to those who are responsible for the health of crews and involved in the promotion of flight safety. Guidelines have been introduced by many countries, but it is important to appreciate that they indicate workloads acceptable to industrial negotiators, and have been arrived at without significant contributions from aeromedical research. The main objective should be to allow crews to adopt an acceptable sleep pattern. It is the preceding duty hours and the duty hours expected over the next few days which are the important considerations. Duration of individual periods of work have some relevance, but minor changes are unlikely to be of much benefit to aircrew or to improve air safety.

TABLE II

Duty Hours within Schedules of Defined Length of Optimum and Maximum Workloads

Days on route	*Duty hours*	
	Optimum workload	*Maximum workload*
2.0	26	29½
3.0	32	36
4.0	37½	42
5.0	42	47
6.0	46	51
7.0	50½	55
8.0	54	58½
9.0	57	62
10.0	60½	65
11.0	63½	68
12.0	66½	71
13.0	70	74
14.0	73	76½
15.0	76	79
16.0	79	82

TABLE III

Duration of Schedules for Total Duty Hours at Optimum and Maximum Workloads
Proposed Duration of Schedule (hours)

Total duty hours	*Optimum workload*	*Maximum workload*
30	64	–
40	109	88
50	165	138
60	237	202
70	312	280
80	–	368

CHAPTER 7

DISORDERS OF SLEEP AND AROUSAL

In the world of aviation irregularity of work is inevitable and there are many reasons why it may be difficult to sleep at times outside the normal rest period. It must, of course, be borne in mind that there is a gradual deterioration in sleep with age. There is little evidence of change in sleep onset latency or in total sleep time during the main span of life, but awakenings during the night are more frequent over the age of 40 years. Drowsy sleep increases steadily and wakefulness increases rapidly after the age of 50 years. The deeper stages of sleep are fairly constant during the early years of life, but are less prominent from 20 years onward, and continue to fall throughout life for both sexes, though the change is more pronounced in males. After 30 years fewer men than women have stage 4 sleep, and in males over 70 years it has almost certainly disappeared.

However, even in a group of apparently healthy individuals sleep difficulties may hide pathology. Disorders of arousal and sleep should be considered when there is a complaint of excessive day time sleepiness or unusual problems in coping with altered time schedules. Much interest has been shown in recent years in disorders of sleep and arousal, and these include disturbances of the sleep-wakefulness continuum related to the circadian rhythmicity of man. Some familiarity with these disorders is essential in understanding insomnia and day time sleepiness, and these symptoms, can be used to classify disorders, though such a classification tends to be repetitive. In the present handbook (Table IV) we have adopted a traditional approach grouping together disorders of the sleep-wakefulness rhythm, those which can be classified as primary or secondary sleep disorders, and the parasomnias. Uncommon sleep disorders have been omitted, unless they could be particularly important in aviation such as those which may involve impaired alertness or disturbances of consciousness.

TABLE IV

Disorders of Arousal and Sleep

A. Variants of the Sleep-Wakefulness Cycle
   - Short and long sleepers
   - Advanced and delayed sleep phase syndromes
   Non-24-hour sleep and irregular sleep-wakefulness patterns.

B. Primary Sleep Disorders
   - Insomnia and hypersomnia
   - Narcolepsy
   - Sleep apnoea
   - Nocturnal myoclonus and restless legs syndrome

C. Secondary Sleep Disorders
   - Medical
   - Behavioural
   - Psychiatric
   Environmental
   - Toxicological

D. Parasomnias
   - Somnambulism (sleep walking) and Sleep talking
   - Sleep terrors
   - Enuresis
   - Nightmares
   - Bruxism (teeth grinding)

VARIANTS OF THE SLEEP-WAKEFULNESS CYCLE

These conditions involve unusual times of sleep onset or waking.

Short and Long Sleepers

Individuals whose sleep within 24 hours is substantially shorter or substantially longer than the average amount for their age, and whose sleep is unbroken and normal, without complaints about sleep, morning alertness, daytime sleepiness or performance, fall into this group. Short sleepers are those who sleep less than three-quarters of the norm and may even sleep less than 3 hours each day. Long sleepers sleep at least 9 hours a day

possibly between 12 and 14 hours. They enjoy and protect their sleep, and so may have difficulty in coping with restricted sleep schedules. Overall there is no underlying pathology, though psychological types are believed to exist by some workers. Short sleepers may have a tendency to hypomania and tend to be efficient and non-worriers. Long sleepers may tend to worry and may be either mildly depressed or anxious.

Delayed and Advanced Phase Syndromes

Disorders of sleep may arise from a misalignment between the sleep-wakefulness cycle of the individual and the circadian changes of the environment. They are essentially abnormalities of the individual's sleep-wakefulness rhythm, and include the delayed and advanced sleep phase syndromes in which sleep onset and wake time are later or earlier than desirable. Sleep occurs at the same clock time each day, and there is no difficulty in maintaining sleep once it has begun. The delayed sleep phase syndrome which is usually seen in young people often presents with the complaint of difficulty in falling asleep at the conventional time. They may also have problems with getting up in the morning and if their sleep is curtailed daytime sleepiness may appear secondarily. The advanced sleep phase syndrome is less common and does not interfere with daytime alertness. The complaint is that of an inability to stay awake in the evening and to maintain sleep until the conventional morning hour.

Non-24-hour Sleep and Irregular Sleep-Wakefulness Patterns

An incremental pattern of delay in the onset of sleep and waking time so that sleep and wakefulness occur at a later clock time on successive days is termed non-24-hour sleep. The condition reflects the inherent circadian sleep-wakefulness period length in individuals which is around 25 hours. An irregular sleep-wakefulness pattern involves disorganised and variable sleep and wakefulness. There is a loss of an entrained 24 hour rhythm, and there are frequent daytime naps at irregular times and excessive bed-rest. Sleep at night is not adequate though the total amount of sleep within 24-hours may appear normal.

PRIMARY SLEEP DISORDERS

Insomnias and Hypersomnias

Although most insomniacs have medical, psychiatric or behavioural problems, a minority have poor sleep in the absence of other significant pathology. In primary insomnia, there is an inability to obtain sufficient sleep. It may vary from mere restlessness to continued wakefulness. It does not involve psychopathology, but may include emotional problems. In some there may be abnormalities of the sleep electroencephalogram such as mini-arousals and fewer sleep spindles.

Some patients, perhaps 20% of those complaining with insomnia, claim that they sleep little or not at all, even though observers find them sleeping soundly throughout the night and there are no changes in the sleep electroencephalogram. This condition is called pseudo-insomnia. There is a tendency to label these as malingerers, but care should be taken in this diagnosis.

In REM interruption insomnia patients habitually wake about 1½–2 hours after sleep onset, and then at regular intervals during the night. Sleep electroencephalography shows that the patient awakes slightly before or just after the onset of each period of rapid eye movement sleep.

The so-called neutral state syndrome – a rare condition – involves excessive daytime sleepiness with automatic behaviour, blackouts and lack of alertness. Electroencephalography shows microsleeps during the day and micro-awakes during the night.

In the condition known as periodic hypersomnia patients present a history of excessive sleep over periods of days, weeks or even months which alternates with normal or even excessively short sleep. The condition may be associated with menstruation.

Narcolepsy

Narcolepsy is a syndrome in which the patient suffers from excessive daytime sleepiness and one or more of three other well established symptoms. A fifth symptom may be added – that of disturbed nocturnal sleep. Probably only 1 in 10 patients with narcolepsy suffer from the complete tetrad, and symptoms related to wakefulness are the more frequent. The primary and

most disabling symptom is drowsiness which results in short periods of daytime sleep. These attacks of daytime sleep, which may sometimes be prevented by concentrating on staying awake, occur at inappropriate times and last for 10–15 minutes, though if the patient is resting they may sleep for a couple of hours, and may or may not awaken refreshed. The attacks may occur with or without warning, and are common in situations which provoke drowsiness in normal subjects such as after lunch and during afternoon lectures.

The most common auxiliary symptom related to the waking state is cataplexy. It occurs in some form or another in at least two-thirds, perhaps all, of patients with narcolepsy. When fully conscious, patients may suffer from a sudden decrease or abrupt loss of muscle tone, which may be generalised or limited to certain muscle groups. This may result in transient weakness of the jaw or in extreme cases complete loss of muscle tone leading to a postural collapse. The deep tendon reflexes are lost and the H-reflex is absent. An attack may last for only a few seconds, and is frequently triggered by exercise and expressions of emotion such as laughing or crying. It may occur many times a day, or once a week or even less. The latter part of the attack can pass smoothly into rapid eye movement sleep, and the underlying mechanism may well be a dissociation between the peripheral and central manifestations of rapid eye movement activity. Cataplexy appears after sleep attacks are established.

Sleep paralysis and hypnagogic hallucinations occur while the subject is falling asleep or on waking, and recordings during these phenomena also reveal REM sleep. In sleep paralysis the patient feels he cannot move any muscles except those controlling the eyes, and this state is often accompanied by an intense feeling of fear and by hypnagogic hallucinations. Respiration is not affected, and the paralysis can be terminated by vigorously moving the eyes or by being touched. It lasts from a few seconds to several minutes. Hypnagogic hallucinations are vivid, frightening auditory and/or visual hallucinations experienced when fully conscious, they often occur during an episode of sleep paralysis. Sleep paralysis and hypnagogic hallucinations are each present in about a quarter of patients with narcolepsy.

Sleep Electroencephalography. Narcoleptics, particulary those in whom excessive daytime somnolence is accompanied by

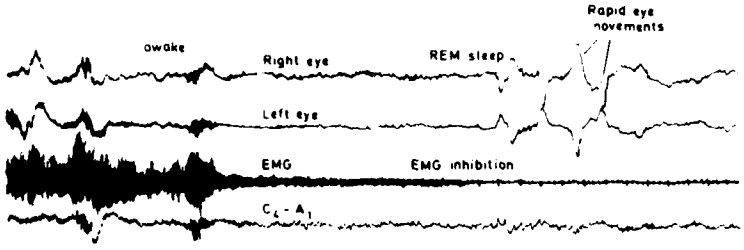

Fig.21 Recording during sleep onset in a narcoleptic subject. The immediate appearance of rapid eye movement sleep (rapid eye movements and loss of electromyographic activity) is characteristic of this condition
Reproduced from Hauri, P. (1977), The Sleep Disorders. By kind permission of the Upjohn Company, Kalamazoo, Michigan

cataplexy, often have a rapid eye movement period immediately at sleep onset (Fig.21), and sleep is often disturbed with awakenings and body movements, excessive drowsy sleep and little slow wave sleep. Some patients may have excessive amounts of rapid eye movement sleep, though usually the duration is within normal limits. As far as diagnosis is concerned a REM period within 10 minutes of sleep is usually considered as evidence for narcolepsy, and rapid eye movement sleep onset may also be observed during daytime sleep. Indeed, the diagnosis is made when sleep onset involves rapid eye movement activity together with sleep attacks and an auxillary symptom. Narcolepsy appears to be a disturbance of sleep involving the rapid eye movement system as well as that concerned with wakefulness.

The incidence of narcolepsy is probably between 1 and 2 per thousand of the population, and it manifests itself during the second or early part of the third decade of life, even though there may be a genetic basis. There is no consistent psychopathology associated with the syndrome, though the patient may be considered as lacking motivation and interest in his work, and often the history of a narcoleptic will include episodes of a disciplinary nature. Treatment is somewhat uncertain though excessive daytime sleepiness may be alleviated by stimulants, and

if the cataplexy is of a serious nature, a tricyclic antidepressant without sedative activity may be used.

Sleep Apnoea

The hypersomnia-sleep apnoea syndrome is found almost entirely in males particularly between the ages of 40 and 60, where its incidence may reach 5% of the insomniac population. It is characterised by excessive daytime sleepiness (hypersomnia) and frequently recurring apnoea during sleep. The syndrome can usually be recognised because of the history of loud intermittent snoring. To diagnose the syndrome at least 10 apnoeic episodes (cessation of airflow at the level of the nostrils and mouth lasting at least 10 seconds) must be observed an hour in both REM and NREM sleep, some of which must occur repetitively in NREM sleep during a 7-hour nocturnal sleep period, as in normal individuals apnoeic episodes may occur at sleep onset or accompany bursts of rapid eye movements. The condition has been separated into two broad complexes. In central apnoea there is an absence of respiratory effort with cessation of diaphragmatic movement, though the upper airway remains open even though there is no airflow. In the other variety upper airways obstruction is present. The airway is closed and there is excessive respiratory effort. The condition may be associated with the development of hypertension with cor pulmonale, and is often associated with severe cardiac arrhythmias.

Because of disturbed noctural sleep or hypoxaemia patients complain mainly about excessive daytime sleepiness, and may take frequent though unrefreshing naps during the day – often at inappropriate times. The football fan may fall asleep at the match and the teacher may fall asleep in front of the class. Obesity, in particular, and possibly depression may be associated with the condition. Nearly all patients are heavy snorers and the diagnosis must be considered in a patient who snores and complains either of excessive daytime sleepiness or insomnia. Heavy snoring may have been present for many years before the development of the condition. Investigation should include both sleep studies and respiratory function tests during sleep. Electroencephalographically, patients may have short sleep latencies and wake up several times during the night (Fig.22). During the day there is sleepiness and long unrefreshing naps. There may be mechanical abnormalities of the soft palate and jaw or even

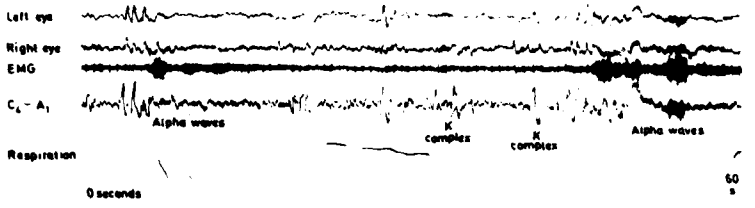

Fig.22 Sleep apnoea: The patient is awake during the period of alpha activity. As he falls asleep (appearance of K complexes and relaxation of the electromyogram) breathing is arrested. When breathing restarts there are electroencephalographic signs of arousal (alpha waves)
Reproduced from Hauri, P. (1977) by kind permission of The Upjohn Company

neurological disorders. If these cannot be corrected or there are no mechanical difficulties a tracheostomy which is opened during sleep may be necessary. Weight reduction and sleeping on the side may help some patients. The possible usefulness of clomipramine is being investigated. Sleep apnoeas are worsened by alcohol and by the benzodiazepines.

The alveolar hyperventilation syndrome is a disturbance of sleep due to ventilatory impairment. Ventilatory studies reveal unresponsiveness to chemical control of ventilation during wakefulness and sleep, though pulmonary function tests are normal. During sleep the tidal volume decreases with hypercapnia and hyperoxaemia.

Nocturnal Myoclonus (periodic leg movements) and Restless Legs Syndrome

In nocturnal myoclonus highly stereotyped leg twitches repeat themselves every 20–40 seconds during sleep. Recordings from the right and left anterior tibialis muscles usually show bursts of activity, and the episodes last from 5 minutes to 2 hours and alternate with normal periods of sleep (Fig.23). In some individuals there are complaints of insomnia. The condition is quite distinct from the startle movements experienced frequently by many people as they fall asleep.

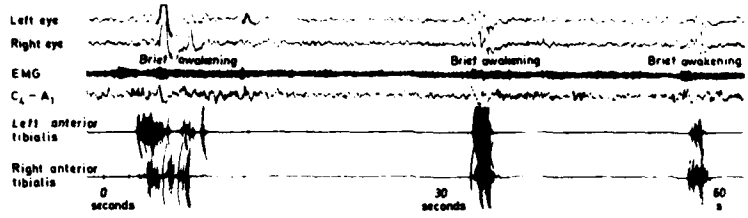

Fig.23 Nocturnal myoclonus, the sleep electroencephalogram indicates stage 2 sleep. There are periodic twitches, every 20–40 seconds in the tibialis muscles, and each is accompanied by a brief awakening
Reproduced from Hauri, P. (1977) by kind permission of the Upjohn Company

Many patients with periodic leg movements when asleep also complain of restless legs before falling asleep. There are uncomfortable and disagreeable sensations of cramp deep inside the calf muscles. The sensations may be ameliorated by movement of the legs but this prevents sleep onset. Some patients are helped by the muscular relaxation induced by benzodiazepines. Montoneurone disease, iron, calcium and vitamin E deficiencies as well as chronic uraemia may be associated with the condition.

SECONDARY SLEEP DISORDERS

Medical

One of the commonest causes of insomnia is pain, but almost any medical condition may be associated with insomnia. Sleep may be impaired with injury, infections and degenerations of the central nervous system, as well as with some forms of epilepsy. Nocturnal migraine sufferers may wake from headaches which appear to develop during REM sleep. Hyperthyroidism and uraemia are associated with short fragmented sleeps, and patients with hyperthyroidism may also show excessive slow wave sleep. *Hypothyroidism may* be associated – though rarely – with excessive daytime sleepiness and the electroencephalogram may show less slow wave sleep. Ischaemic heart disease frequently results in sleep disturbance. Patients who awaken in the night with angina usually awake from a REM period. Cardiac

arrhythmias also occur more often in REM than during NREM sleep.

Behavioural

A large number of insomnias are related to the problems of life. Trying too hard to sleep (internal arousal), difficulties with sleeping after a period of emotional turmoil (conditioned insomnia), and phobia of sleepless nights all contribute to poor sleep. Indeed, sleep problems of a behavioural origin may lead to reduced alertness and complaints of lassitude. Chronic anxiety or a conditioned reinforcement of sleep difficulties lead to more persistent sleep problems. Patients often consider themselves as light sleepers and have multiple somatic complaints leading to abuse of alcohol and hypnotics. Persistent insomnia arising in this way is common. Excessive daytime sleeping and napping may be seen in some patients who have difficulty in coping with life.

Psychiatric

Psychiatric patients often have severe insomnia, and the possibility of an underlying depressive illness must always be considered. Patients with anorexia nervosa tend to have disturbed sleep particularly in the middle third of the night and wake early. This pattern is unrelated to mood but probably to the severity of the nutritional disturbance.

Fragmented sleep is well known in depression, though some depressives sleep quite normally and others for excessively long times. It is unlikely that sleep laboratory studies can differentiate between reactive and endogenous depression, though the complaint of early morning awakening is more likely to be associated with endogenous depression. Slow wave activity is usually reduced even when sleep is of normal duration, and although REM sleep is not shortened, in endogenous depression there may be an early onset of the first REM period. Deprivation of REM sleep has been used in the treatment of this condition as well as changing the time of the onset of sleep. Patients with bipolar depression (manic depressive syndrome) usually sleep more when depressed and less when manic when they have problems in falling sleep. They can also present with insomnia during the depressive phase

There is probably no specific sleep pattern associated with schizophrenia. The sleep of the chronic schizophrenic may be adequate though during acute episodes it is usually disturbed. There may be a severe sleep onset insomnia often with difficulty in sleep continuity and perhaps daytime sleepiness may be present.

Environmental

Insomnia and daytime sleepiness may be associated with a variety of environmental factors, though individual susceptibility is an important factor. Sleep may be influenced by exercise during the day, by noise and by physical surroundings, by temperature and by diet. Losing weight is associated with sleep disturbance and the converse is true for those gaining weight. Within the environmental factors one must consider the disturbances brought about by world-wide travel and by shiftwork, but these are dealt with elsewhere.

Toxicological

Sleep disturbance is associated with tolerance to or withdrawal from central depressants. With continued use, usually for at least 30 days, tolerance develops and the drugs become less effective, often leading to increased doses. With the chronic use of an hypnotic sleep may be marked by disruption of its normal architecture and by frequent awakenings lasting for 5 minutes or more (Fig.24). This may be a particular problem during the latter half of the night. When the drug is suddenly discontinued severe sleeplessness may supervene perhaps accompanied by the general features of a withdrawal syndrome.

There is the possibility that long-term therapy even with benzodiazepines may lead to unwanted effects when the treatment is discontinued. With benzodiazepines which have long-acting metabolites such as desmethyldiazepam and desalkylflurazepam, the reappearance after an abrupt discontinuation of pre-treatment symptoms of anxiety and insomnia may be slower than that with short-acting compounds, though this may not always be the case. There is at present some uncertainty concerning the nature of rebound insomnia and rebound anxiety though they would appear to be related to the regular use of relatively high doses for unnecessarily long periods of time.

Fig.24 Hypnograms in a young adult with insomnia on 100 mg secobarbital.

A. Hypnogram of a healthy young adult similar to that seen in Figure 9

B. Sleep of a young insomniac without medication. There is a delay to sleep onset and there are frequent and prolonged awakenings. Rapid eye movement sleep is also delayed and its duration is reduced

C. During the first night on medication (secobarbital 100 mg) the pattern of sleep onset is normal, but there is a continued delay to rapid eye movement sleep. However, the frequent and prolonged awakenings seen before medication have disappeared

D. After five nights on the drug the pattern of sleep seen before medication has returned. There is a long latency to stage 2 sleep and there are frequent awakenings

E. Sleep during the first night after withdrawal of medication. There is a very long latency to stage 2 sleep with frequent awakenings

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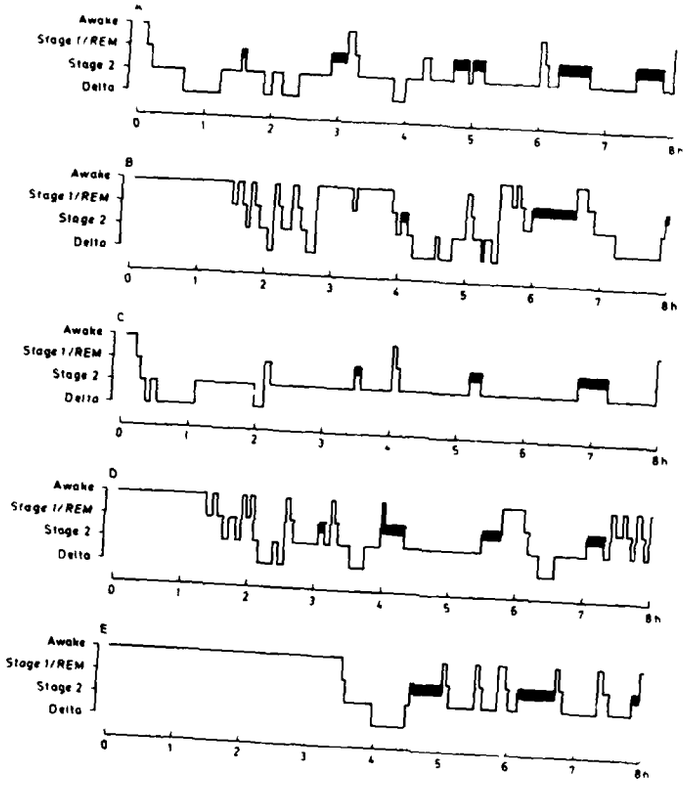
A
Awake
Stage 1/REM
Stage 2
Delta
0 1 2 3 4 5 6 7 8h
B
Awake
Stage 1/REM
Stage 2
Delta
0 1 2 3 4 5 6 7 8h
C
Awake
Stage 1/REM
Stage 2
Delta
0 1 2 3 4 5 6 7 8h
D
Awake
Stage 1/REM
Stage 2
Delta
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Stage 2
Delta
0 1 2 3 4 5 6 7 8h

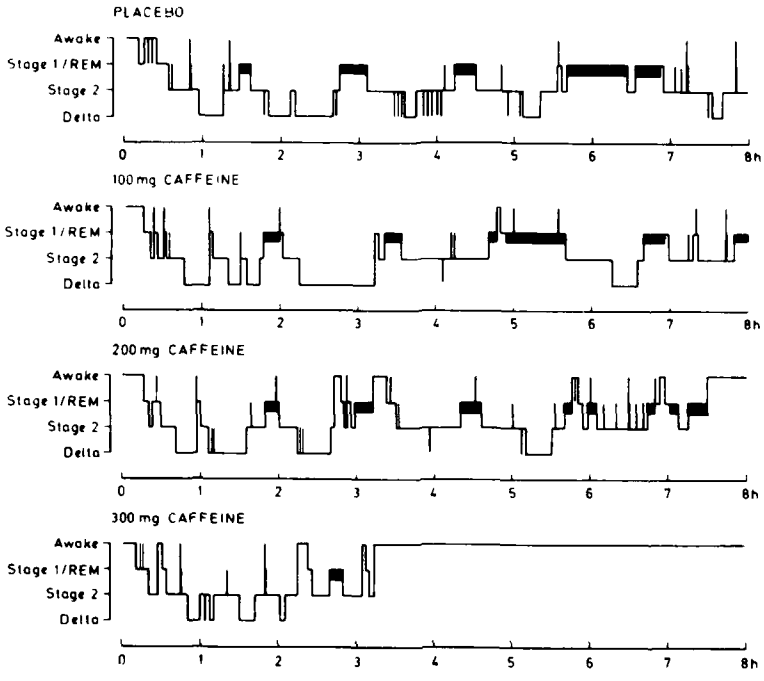

Fig.25 Effect of caffeine (100, 200 and 300 mg) on the sleep of a healthy young adult. Sleep structure is not changed, but with increasing doses there are more awakenings. With 300 mg there is sustained wakefulness after a short period of sleep

The sustained use of stimulants including quite normal amounts of caffeine often taken late in the evening, may also give rise to disturbed sleep (Fig.25). Poor noctural sleep may increase the tendency to take stimulants during the day so as to maintain alertness. In individuals dependent or habituated to stimulant drugs withdrawal may present as daytime sleepiness, frequent napping and long periods of nocturnal sleep.

The ingestion of even a small amount of alcohol tends to alter sleep. Sleep onset may be shorter, but there may be more awakenings and stage changes (Fig.26). It also tends to depress REM sleep. The chronic alcoholic awakens many times during

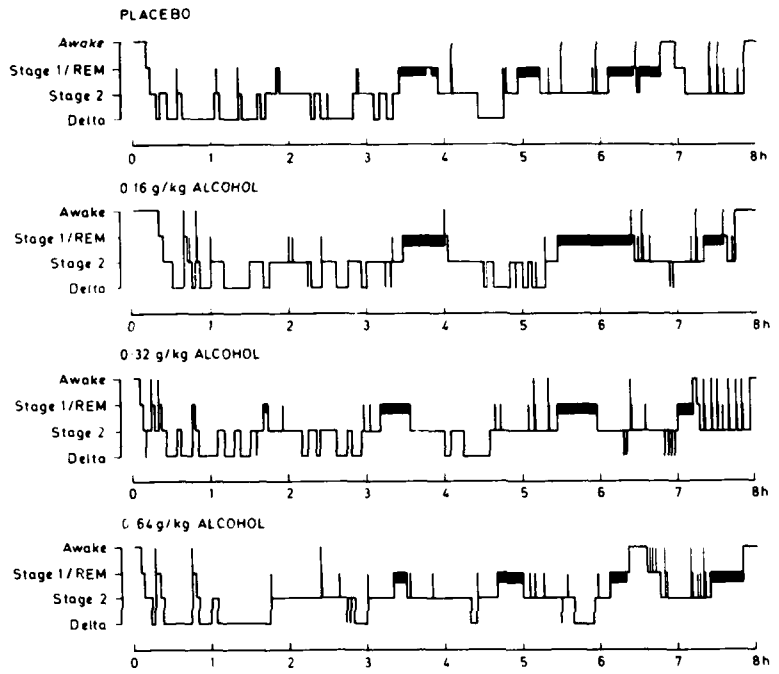

Fig.26 Even in small doses alcohol may disturb sleep. The disturbance may involve delay to rapid eye movement sleep, and frequent arousals during the latter part of the night

the night and has more stage changes with little or no slow wave sleep. Time in bed may be increased and the patient may experience excessive daytime sleepiness with numerous naps. Insomnia is also a feature of withdrawal from alcohol, and some patients may show continuous REM activity. It must also be remembered that even after a long period of abstinence unusual sleep patterns may persist in the alcoholic who may still complain of difficulty in falling asleep.

Toxicity must always be considered as a possible cause of sleep problems. Arsenic, mercury, copper, carbon monoxide poisoning as well as exposure to radiation, and the possibility of narcotic abuse must not be overlooked.

PARASOMNIAS

These conditions occur far more often in children than in the adult and are usually seen early in the night when slow wave sleep is most prominent, though some occur in the transition between sleep and wakefulness. Individuals are often difficult to arouse during the unusual behavioural activity and rarely recall the incident. Essentially they are dysfunctions associated with sleep and partial arousal, and are not disorders of sleep and wakefulness *per se*.

Somnambulism (sleep walking). Somnambulism is observed in the first third of the night when slow wave sleep predominates. The patient may leave the bed and walk about. Somnambulism is quite common in children. There may be psychological problems amenable to psychotherapy and temporal lobe epilepsy, although rare, must be excluded. Treatment should be directed toward the prevention of accidents. Sleep-talking also occurs during NREM sleep.

Sleep Terrors (paver nocturnus). A sleep terror is an arousal from slow wave sleep in the first third of the night inaugurated by a scream or cry and accompanied by anxiety or even panic. It occurs most often in children.

Enuresis. Enuresis during sleep is related to slow wave activity, and in a child over 3 years old with previously well established habits needs investigation.

Nightmares. These involve the recall of disturbing dreams while awakening from REM or light non-REM sleep.

Bruxism (excessive tooth grinding). Bruxism is related to a general lightening of sleep and can lead to dental abnormalities.

SUMMARY

This brief review of the disorders of sleep may help in the initial investigation of insomnia and excessive day time sleepiness. It is always important to explore a possible behavioural or psychiatric background, and to exclude a medical, especially an endocrine or neurological, cause. In patients with excessive day time sleepiness simple questions are likely to uncover the diagnosis in three-quarters of cases. Attacks of muscle weakness in young adults suggest narcolepsy and a history of snoring

suggests sleep apnoea, while the misuse of drugs must always be borne in mind. Unusual patterns of sleep and wakefulness also lead to day time sleepiness. Most certainly excessive day time sleepiness should not be taken too lightly. Complaints related to sleep are often exaggerated but at least in aviation, they should not be dismissed too quickly because of their potential operational significance.

CHAPTER 8

HYPNOTICS

The management of sleep difficulties which arise from irregularity of work must be related to the cause, but the aeromedical specialist is frequently faced with the possible use of hypnotics. There are no simple guidelines, but an understanding of the various issues involved will help toward the wise use of these drugs in those who have to cope with irregular rest and carry out skilled activity. Some knowledge of pharmacokinetics is useful as persistence of effect and the potential for accumulation with repeated ingestion are important factors, while efficacy in relation to sleep at unusual times must also be considered.

PHARMACOKINETICS

Distribution and Elimination

The way in which an hypnotic is distributed in the body involves a central compartment of blood and highly vascular tissues such as the heart, lung and liver, and a peripheral compartment of lesser vascularity such as voluntary muscle. The brain is also a highly vascular organ, and as hypnotics usually cross the blood-brain barrier with ease it is also considered part of the central compartment. When a drug is given intravenously there is for all practical purposes instantaneous mixing, and the changes in plasma concentration, which are usually assessed by measurement of venous plasma, may indicate the parts played by the central and peripheral compartments if the decay follows two clearly defined phases – both of which are exponential. However, when it is given orally or intramuscularly plasma concentrations are influenced by absorption, and so there is also a growth phase. It is absorption rather than penetration of the blood-brain barrier which tends to limit the rate of transfer of an hypnotic to its site of action.

The first part of the decay of the plasma concentration relates primarily to distribution and so to penetration of the peripheral compartment, while the second part relates to elimination by metabolism and/or by excretion from the central compartment (Fig.27). Tissue penetration and elimination occur

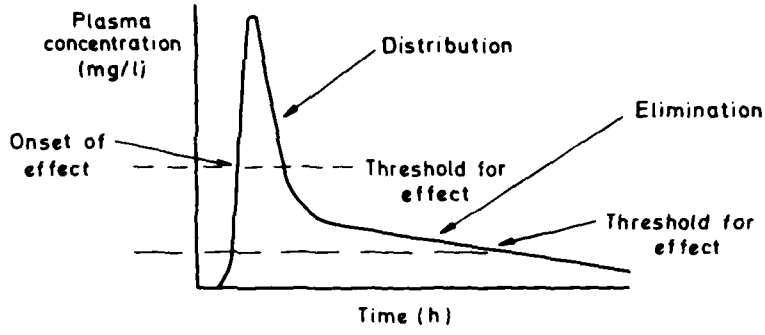

Fig.27 Plasma concentration profile (semi-log plot) for a drug with a biexponential decay after oral dosing. There is an effect as long as the concentration remains above a certain level. The threshold may be related to the distribution or elimination phases. If it is above the concentration at which the inflexion of the distribution and elimination half-lives occurs then it will be related to the distribution phase and any effect will be of short duration

together, and the curve reflects the relative dominance of these events at different times. A drug has an effect as long as its concentration remains above a certain plasma level. If the threshold is reached during the phase which predominantly represents distribution and this part of the decay is usually rapid then the duration of action is likely to be short, but if the threshold is related to the elimination phase then it will be much longer - particularly if this phase is prolonged.

It is evident that both distribution and elimination influence duration of activity, though a relatively short duration of action may be attained even though elimination is relatively slow. In principle two conditions are required. The drug must become available in the blood in relatively high concentrations soon after administration, otherwise the concentration profile will level out and no distinction will be found between the faster distribution and slower elimination phases. High concentrations such as those seen after intravenous injection can be achieved by drugs which are rapidly absorbed. Secondly, the drug has to cross the blood-brain barrier rapidly, and with hypnotics brain concentrations follow closely those of the plasma.

Intermittent Therapy and Accumulation

These various pharmacokinetic aspects are important in the appropriate use of hypnotics. With oral ingestion the major determinant of the onset of action of a single dose is absorption. Rapid absorption is associated with a quick onset of action, whereas with slow absorption activity may be attenuated or even eliminated. When a drug is taken as an hypnotic rapid absorption is desirable, whereas a slower absorption rate may be preferred if a sustained anxiolytic effect without immediate drowsiness is sought.

In the management of sleep difficulties an intermittent type of drug action may be desirable even when the drug is given daily. The theoretical plasma profile levels of two hypnotics with very different half-lives are illustrated in Figure 28. When given every 24 hours a drug with an elimination half-life of 24 hours or longer will accumulate, but one with a half-life of 6 hours will not, and this ensures the intermittent type of action. However, clinical effects may not relate directly to plasma concentration.

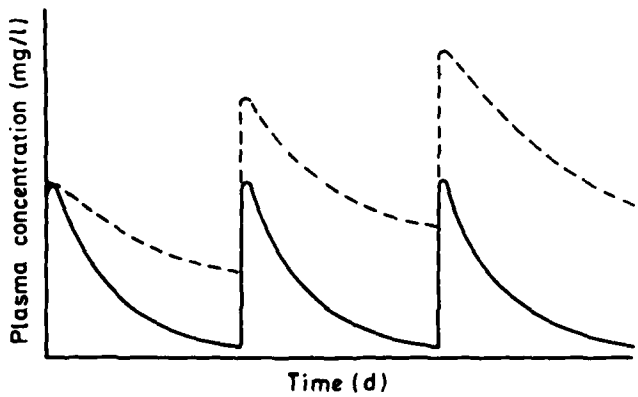

Fig.28 Plasma concentration profiles of two hypnotics with different elimination half-lives (lower curves – 6 h; upper curves – 24 h) given every 24 hours. If the compound with a half life of 6 h is given daily there will be no accumulation and there will be an intermittent type of drug action. However, the drug with an elimination half-life of 24 h will accumulate with daily ingestion

Tolerance may develop particularly as far as the central nervous system is concerned. Indeed, unwanted drowsiness may be experienced only early on in the course of chronic therapy, though tolerance to the persistent effects of an hypnotic is not a point in favour of its use when there are other suitable hypnotics free of such effects.

The metabolism of long-acting benzodiazepines is likely to be influenced by the age of the patient. Individuals over 60, even when healthy, may have impaired ability to complete the usual biotransformations, and so the half-lives of long-acting benzodiazepines tends to be prolonged in the elderly as opposed to young individuals. Age related decrements can vary from slight to a very marked effect depending on the drug and on the sex of the patient, and metabolic impairment in elderly males may be greater than that in elderly females.

Another question is what happens if the drug is taken daily. The rate of accumulation of a drug varies inversely with the elimination half-life, and so the longer the half-life, the slower the rate of accumulation. In general, steady state conditions are reached after an interval of about four times the half-life. Drugs with long half-lives accumulate slowly but extensively, whereas accumulation, though completed more rapidly, may not be a factor of clinical significance with drugs with shorter half-lives.

PHARMACODYNAMICS

The activity of a drug relates closely to absorption, distribution and elimination as well as to metabolism, and it is useful to follow these events with diazepam as an example. Diazepam is rapidly absorbed. A single dose, say 10 mg, has an immediate effect, which persists for a few hours (Fig.29) even though its elimination half-life ranges from 14–90 hours. This is due to rapid and extensive distribution into the tissues. On the other hand daily ingestion will lead to accumulation both of the parent compound and of its long-acting metabolite, nordiazepam, which also has a long elimination half-life (30–60 hours). Residual sequelae with a single dose of 10 mg diazepam are unlikely, but sustained daytime anxiolytic activity will follow daily ingestion. The pharmacokinetics of lorazepam are different from those of diazepam. With lorazepam the distribution phase is less extensive, and so concentrations above threshold are more likely to be

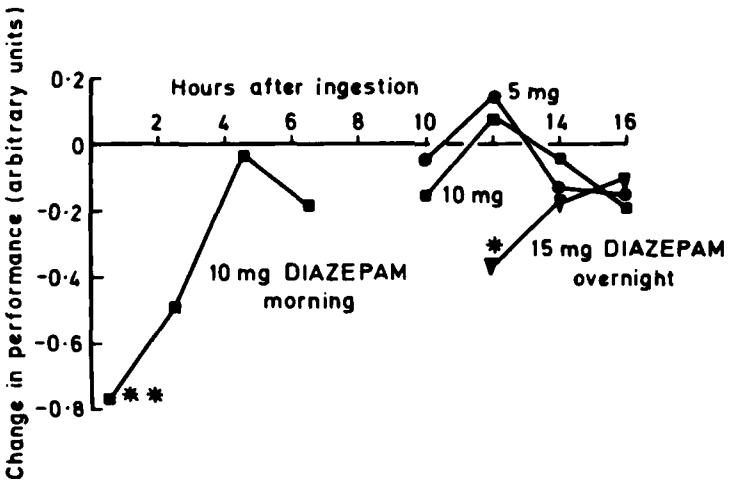

Fig.29 Changes in performance on a visuo-motor coordination task (arbitrary units) after diazepam. Stars refer to the level of significance (5%, 1% or 0.1%) of the difference between performance with diazepam and with placebo. 5–10 mg diazepam overnight is without a residual effect, though it can be seen with 15 mg. Ingestion of 10 mg diazepam in the morning shows that the duration of impaired performance is limited to a few hours, and so likely to be contained by a sleep period. The limited duration of action of a single dose is related to its sustained distribution phase

related to the elimination phase with its half-life of 10–20 hours. Though this is much shorter than that of diazepam, lorazepam may have a more prolonged effect due to the absence of a sustained distribution phase.

The repeated use of benzodiazepines with half-lives of 16–24 hours or longer, of either the parent compound or of an active metabolite, usually lead to persistent activity and this property is relevant to anxiolytic therapy. Nordiazepam, which has a long elimination half life, is a metabolite of several benzodiazepines (Fig.30) and in one, potassium chlorazepate, the parent drug may not even reach the systematic circulation, and serves as a pro-drug or precursor of nordiazepam. However,

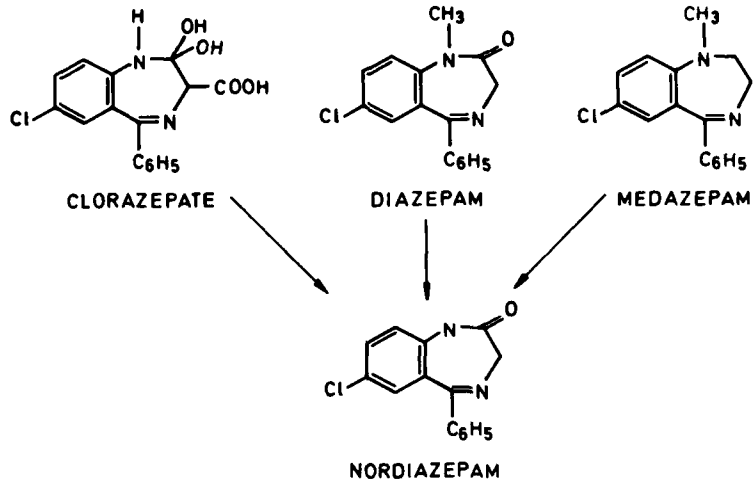

Fig.30 Nordiazepam (N-desmethyldiazepam) is a metabolite of several benzodiazepines. It has a half-life of between 30 and 60 hours – much longer in some individuals. The pro-drugs, potassium chlorazepate, diazepam and nordiazepam, are used as anxiolytics

pro-drugs or precursors with a common metabolite may not have an identical action as the rate at which the metabolite reaches the blood after a single dose may not be the same, and this could give rise to differences in immediate effects. Another drug which is essentially a precursor and has a long-active metabolite is flurazepam.

CLINICAL CONSIDERATIONS

In those whose insomnia is associated with anxiety, the use of benzodiazepines with more persistent activity is appropriate. A single daily dose of diazepam (5–10 mg), potassium chlorazepate (15 mg) or flurazepam hydrochloride (15 mg) at bedtime may be sufficient. Furthermore, the occasional omissions of doses will n ɔt lead to an acute reappearance of symptomatology. However, accumulation may give rise to unwanted daytime drowsiness and impairment of psychomotor performance. With low doses impaired performance the next day

is likely to be minimal, and this may be offset, at least partially, by tolerance, and, in any case, performance in some patients with anxiety may even be improved by therapy.

Though benzodiazepines with persistent effects are useful in anxiety, drugs in which daily ingestion leads to an intermittent type of action are particularly appropriate as hypnotics for those in which psychopathology is not a relevant feature. Active metabolites are less common, and their clinical effect is usually determined by the parent compound. With daily ingestion steady state conditions are reached relatively rapidly, and the washout of the drug after termination of treatment is quicker. Further, the metabolic transformation of some drugs with short half-lives – those which are conjugated with glucuronic acid – do not appear to be influenced by age as much as the longer acting compounds.

RESIDUAL SEQUELAE

Obviously, hypnotics with limited duration of activity are appropriate for those involved in skilled activity and in whom the predominant problem is that of disturbed sleep. However, residual impairment of performance with overnight ingestion may still arise, and it may extend well into the next day even with doses which are within the generally accepted therapeutic range. A variety of tasks have been used to investigate this problem, and there is broad agreement on the relative persistence of the various drugs available. Early studies with the barbiturate, heptabarbitone, which had a limited duration of action showed that decrements in psychomotor performance may persist for 10 hours after 200 mg, 13 hours after 300 mg and 19 hours after 400 mg (Fig.31). It is evident that sequelae are likely to be related to dose both in the extent of the decrement at any given time and in the persistence of the impairment. Impaired performance is more severe and persists far longer with higher doses.

1,4-Benzodiazepines

In the context of hypnotics which may be used safely by those involved in skilled activity, attention has been largely directed toward the benzodiazepines. Impaired performance with a single dose of diazepam is limited – due to its sustained distribution phase – and residual impairment is highly unlikely

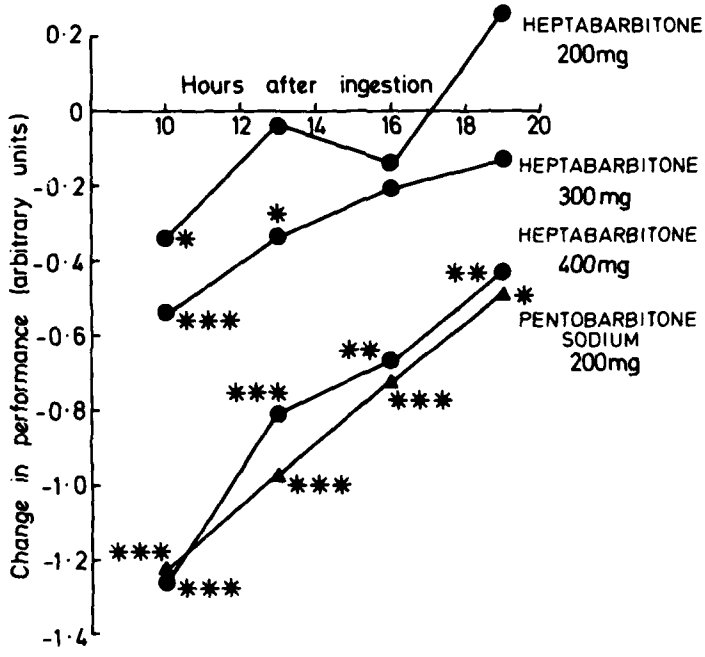

Fig.31 Changes in performance on a visuo-motor coordination task (arbitrary units) after the barbiturates, heptabarbitone and pentobarbitone. Stars refer to the level of significance (5%, 1% and 0.1%) of the difference between performance with drug and with placebo. It can be seen that the severity and persistence of impaired performance is related to dose

with a single dose taken overnight as long as it does not exceed 10 mg. Unfortunately, daily ingestion of diazepam leads to accumulation of the parent compound and of its metabolite, N-desmethyldiazepam, and so residual sequelae are only absent when used occasionally. Nevertheless, it can be suitable for those who carry out skilled activity but it should not be taken more frequently than once every 48 hours and more than twice in 7 days.

The long elimination half-life of diazepam and of its metabolite, nordiazepam, are clearly disadvantages when

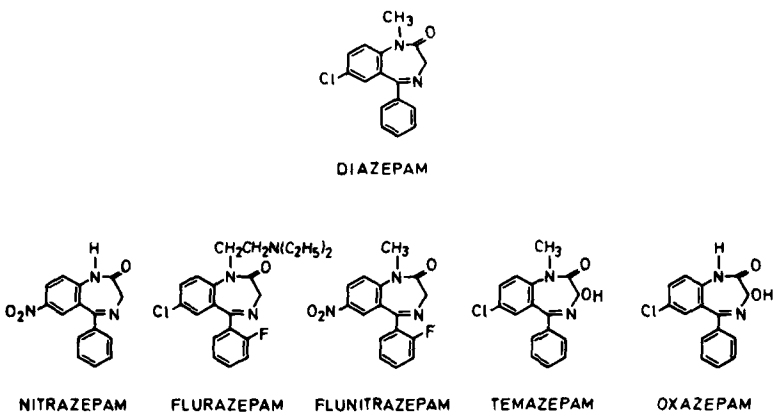

Fig.32 The benzodiazepine molecule has been modified in many ways to optimise its hypnotic potential. The various modifications are related to the molecular structure of diazepam

intended for use in those involved in skilled activity, but the relatively short duration of action of a single dose due to its sustained distribution phase suggested that closely related compounds without long-acting metabolites may have a better profile. Developments have been along two broad lines. Using diazepam as the example (Fig.32), the benzodiazepine molecule has been modified by demethylation (nitrazepam and oxazepam) or substitution of the 1-position (flurazepam hydrochloride), by hydroxylation of the 3-position (temazepam and oxazepam), by substitution of a nitro group in the 7-position of the benzene ring (nitrazepam and flunitrazepam), and by addition of various halogens in the phenyl ring (flurazepam and flunitrazepam).

The hydroxylated metabolites of diazepam, temazepam and oxazepam, which are free of long-acting metabolites, have been studied in detail (Fig.33). Temazepam has a well-defined distribution phase and the elimination phase has a half-life of around 10 hours, while oxazepam has a single exponential decay with a somewhat longer half-life. There are no residual sequelae after overnight ingestion of 20 mg temazepam (Fig.34), though with a higher dose (30 mg) they may appear. With oxazepam, the dose range 15–30 mg is also free of residual effects, though 45 mg leads to an obvious decrement (Fig.35). Oxazepam

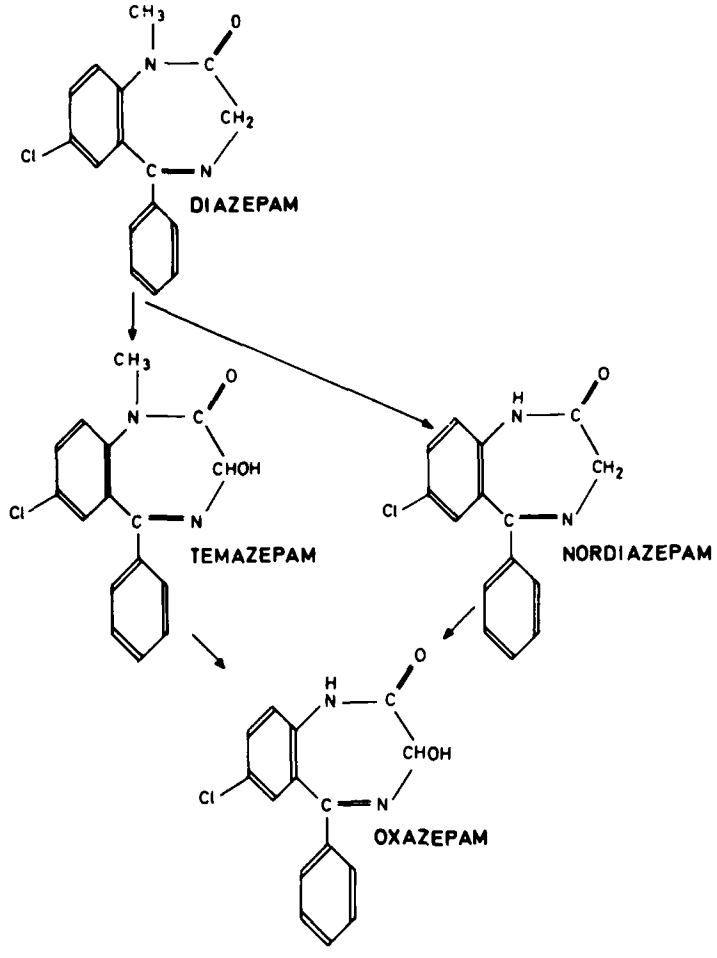

Fig.33 Diazepam and its hydroxylated metabolites, temazepam (3-hydroxydiazepam) and oxazepam (3-hydroxy, N-desmethyldiazepam). Nordiazepam (N-desmethyldiazepam) is also a primary metabolite of diazepam, but has a very long elimination half-life (30–60 h) compared with those of temazepam (5–15 h) and oxazepam (5–20 h)

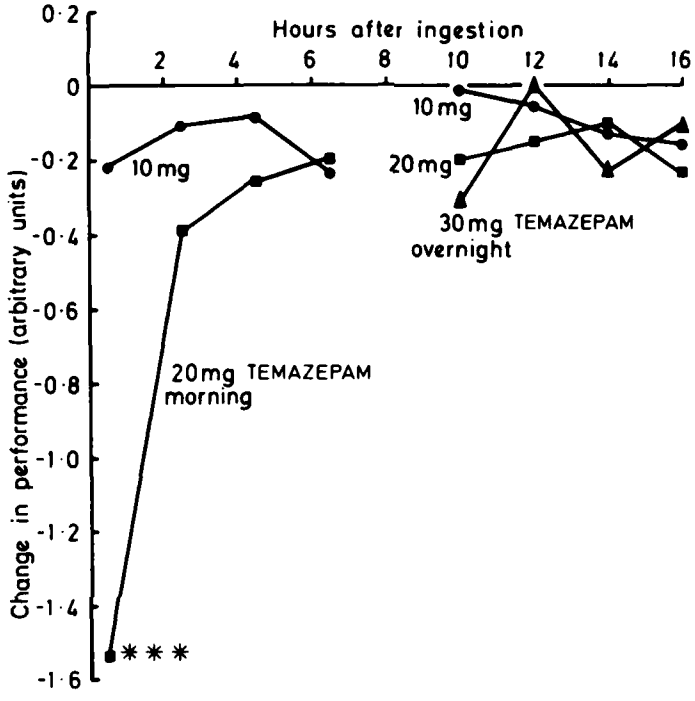

Fig.34 Change in performance on a visuo-motor coordination task (arbitrary units) after temazepam. Stars refer to the level of significance (5%, 1% and 0.1%) of the difference between performance with the drug and with placebo. 10–30 mg temazepam overnight are without residual sequelae, though there is more likelihood of an effect as the dose increases. With 20 mg temazepam the duration of impaired performance is limited to a few hours, and so likely to be contained by a sleep period. The limited duration of action of a single dose is related to its sustained distribution phase

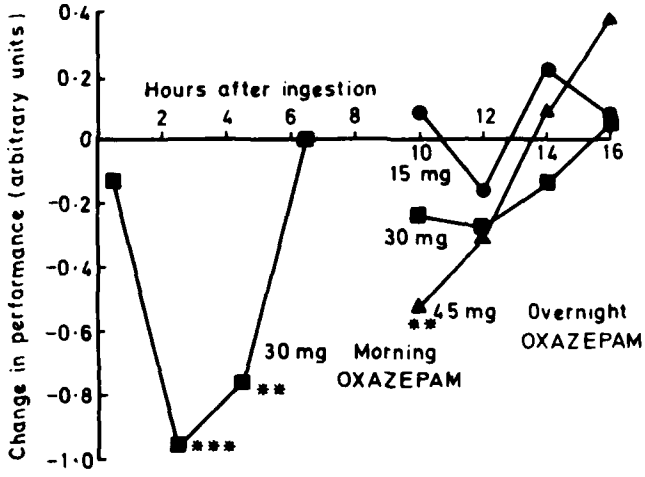

Fig.35 Change in performance on a visuo-motor coordination task (arbitrary units) after oxazepam. Stars refer to the level of significance (5%, 1% and 0.1%) of the difference between performance with the drug and with placebo. 15–30 mg oxazepam overnight are without a residual effect, though there is a clear decrement with 45 mg. With 30 mg oxazepam in the morning onset of impaired performance is delayed, but the duration is limited to a few hours and so still likely to be contained by a normal sleep period. The delay in the onset of impaired performance indicates poor absorption of the drug in the formulation used. In sleep studies oxazepam has little, if any, effect on sleep onset latency

(15–30 mg) has the disadvantage that in the formulations at present available it is slowly absorbed and so is unlikely to be effective when a reduction of sleep onset latency is necessary. Otherwise it is a useful hypnotic.

Triazolo- and Imidazodiazepines

More recently attention has turned toward the triazolodiazepines and the imidazobenzodiazepines. These compounds have heterocyclic ring structures across the 1,2-position, and include triazolam and brotizolam of the

triazolodiazepine group (Fig.36), and midazolam and loprazolam of the imidazobenzo-diazepine group (Fig.37). They have very fast elimination rates and appear to be without long-acting metabolites. Drugs with fast elimination may nevertheless have a slower fall in plasma concentration than the very fast distribution phase of drugs with a clear biexponential decay, and so provide a more sustained activity during the sleep period. Further, the rapid fall in plasma concentration around awakening is quicker than that of the elimination phase of the biexponential compounds, and so residual sequelae, if any, disappear rapidly. In this way drugs with fast elimination may provide a particularly favourable balance between efficacy and residual sequelae.

The plasma decay half-life of triazolam is around 3 hours, and brotizolam which has the same heterocyclic moiety across the 1,2-position, but with the benzene ring replaced by a thieno complex, has a slightly longer half-life. Both are without residual effects on performance in doses up to 0.25 mg (Figures 38 and 39) and accumulation with daily ingestion is highly unlikely. The half-life of midazolam is around 2 hours, and in doses up to at least 20 mg does not lead to performance decrements. Midazolam may prove to be particularly useful for the short periods of rest of shiftworkers.

SLEEP

Hypnotics with dose ranges free of residual sequelae must nevertheless, preserve normal sleep patterns. A drug which can shorten the sleep onset latency and reduce awake activity and possibly drowsy sleep without an adverse effect on sleep architecture is required. Increased total sleep time may not be essential. Diazepam (5–10 mg) and temazepam (10–20 mg) fulfil these requirements. Oxazepam (15–30 mg) is poorly absorbed in the formulation at present available (Fig.40) and does not shorten sleep onset latency. A good profile is provided by triazolam (0.125–0.25 mg), brotizolam (0.125–0.25 mg) and midazolam (10–20 mg), and these drugs are without adverse effects on sleep. However in many drugs the first period of REM sleep may be delayed, and though REM sleep may be reduced during the early part of the night, it is not changed over the whole night.

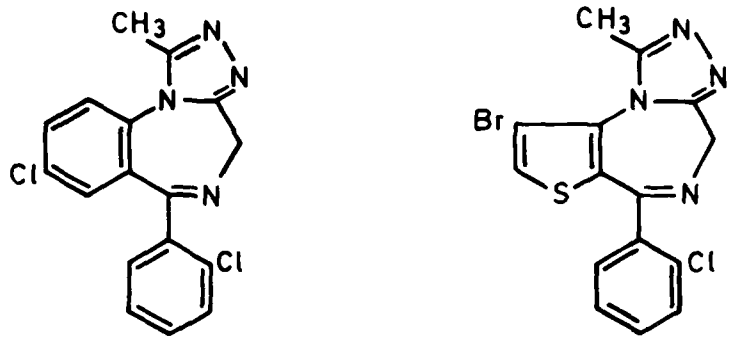

Fig.36 Structural formulae of the triazolo-benzodiazepines. On the left, triazolam and on the right, brotizolam

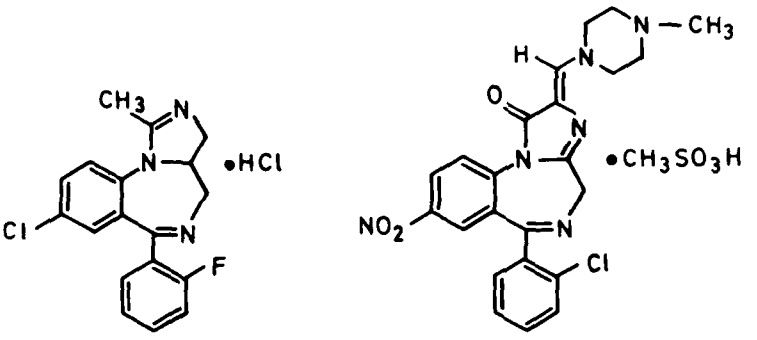

Fig.37 Structural formulae of the imidazobenzo-diazepines. On the left, midazolam and on the right, loprazolam

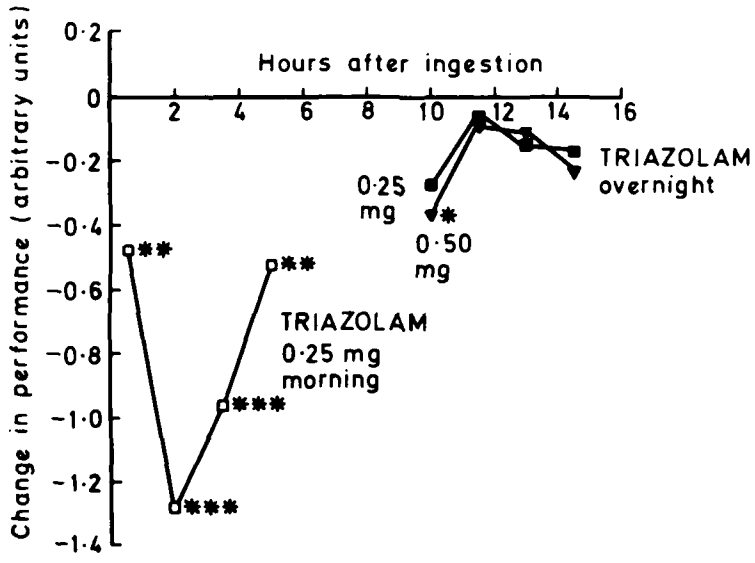

Fig.38 Change in performance on a visuo-motor coordination task (arbitrary units) after triazolam. Stars refer to the level of significance (5%, 1% and 0.1%) of the difference between performance with the drug and with placebo. 0.25 mg triazolam overnight is without a residual sequel, though there may be an effect with the higher dose of 0.5 mg. Ingestion of 0.25 mg in the morning shows that the duration of impaired performance is limited to a few hours, and this is related to its high rate of elimination

Middle Age

In the use of hypnotics in aviation it is important that their efficacy should be maintained over the span of working life. The sleep of middle age is more disturbed than that of the young adult. The sleep period contains more awake and drowsy activity, and so it may be expected that hypnotics would easily improve the sleep of the middle aged. However, diazepam and temazepam are less effective than would be expected from studies with the same drugs in young adults. Essentially, diazepam and temazepam reduce awake activity in middle age.

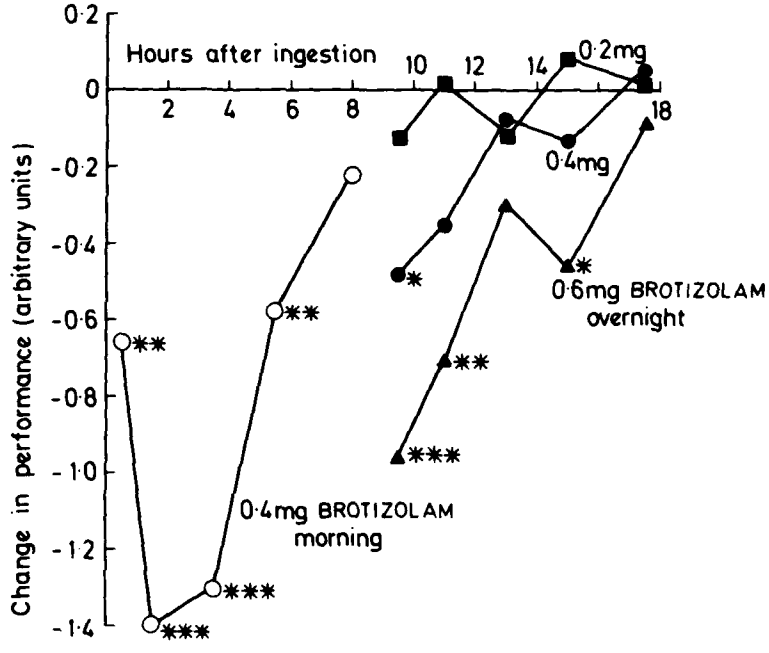

Fig.39 Change in performance on a visuo-motor coordination task (arbitrary units) after brotizolam. Stars refer to the level of significance (5%, 1% and 0.1%) of the difference between performance with the drug and with placebo. 0.2 mg brotizolam ingested overnight is free of residual effects the next morning, but they appear with 0.4 mg, though limited to 10 h after ingestion. With ingestion of 0.4 mg brotizolam in the morning, impairment of performance is limited to a few hours. With brotizolam the overnight ingestion of 0.25 mg is likely to be free of sequelae the next day, and this is related to its high rate of elimination

The possibility that some hypnotics may be less useful in middle age is also supported by studies with other benzodiazepines. Somewhat higher doses may be required by this age group. However, with diazepam doses above 10 mg should not be used, but with temazepam the dose may be extended to 30 mg, and with triazolam 0.375 mg may well be appropriate. These doses

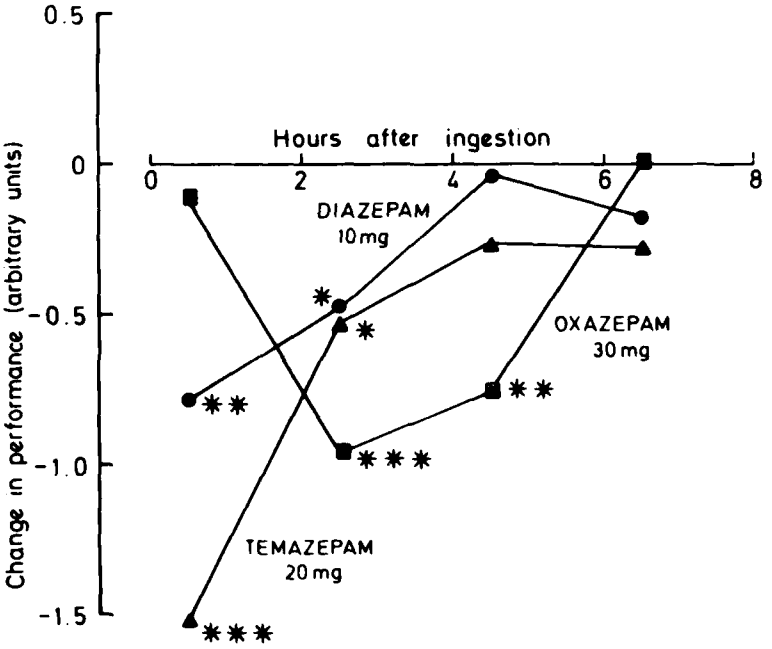

Fig.40 Summary of the persistence of impaired performance with 10 mg diazepam, 20 mg temazepam and 30 mg oxazepam after morning ingestion. Stars refer to the level of significance (5%, 1% and 0.1%) of the difference between performance with the drug and with placebo

are unlikely to lead to performance decrements, and in any case, as they will be used by those over 45 years, the question may not be quite so critical. With brotizolam the dose range, 0.125 0.25 mg, is likely to be acceptable in middle age.

Hypnotics and Shiftwork

Although sleep disturbance associated with shiftwork has been well documented, less attention has been given to the use of hypnotics at unusual times, when the circadian desire for sleep is less particularly during the morning. It is true that an effect on sleep onset latency may not be essential as many shiftworkers experience more difficulty in maintaining sleep than in falling

asleep, but, daytime rest tends to be shorter than night time sleep and so a limited duration of action is essential.

Diazepam reduces awake activity and improves the efficiency of day time sleep, and in doses up to 10 mg is unlikely to impair performance beyond the sleep period. Temazepam may be less effective for sleep during the day. Oxazepam, despite its slow absorption, is useful if there are no difficulties with sleep onset. The effect of flunitrazepam (0.25, 0.5 and 0.75 mg) on sleep during the day is illustrated in Figure 41, and provides an indication of the way in which daytime sleep may be improved by hypnotics. However, interest now centres on the triazolo- and imidazo-diazepines for the management of sleep disturbances in shiftworkers. These are likely to be particularly suitable for sleep during the day, as they have fast elimination. Doses of 0.125 mg triazolam and brotizolam are indicated, at least initially, for the shorter periods of sleep which are seen in shiftworkers, and would certainly be free of residual sequelae. Midazolam (10–20 mg) is also promising, and more information is needed on this drug.

SUMMARY

It is evident that much progress has been made over the past few years in the development of hypnotics which can be used for those involved in skilled activity. However, because of the critical nature of the requirements in aviation, more information is needed, not only on the use of some of these drugs in the management of normal patterns of rest and activity, but also the management of irregular patterns of rest associated with shift-work. There is a wide choice, though the disadvantages of some drugs must be borne in mind. Diazepam (5–10 mg) is an excellent hypnotic when used occasionally for both night time and day time sleep, but it should not be ingested more than once every 48 hours and more than twice in 7 days. Temazepam and oxazepam are also useful, but temazepam (10–20 mg) may be less effective when the rest period does not coincide with the circadian desire for sleep, and oxazepam (15–30 mg) is unlikely to shorten sleep onset. Triazolam (0.125 0.25 mg) can be used *daily – if this is essential* – and this is so with the other triazolodiazepine, brotizolam (0.125–0.25 mg). Midazolam (10–20 mg) with its very short elimination half-life is a promising hypnotic in the context of shiftwork.

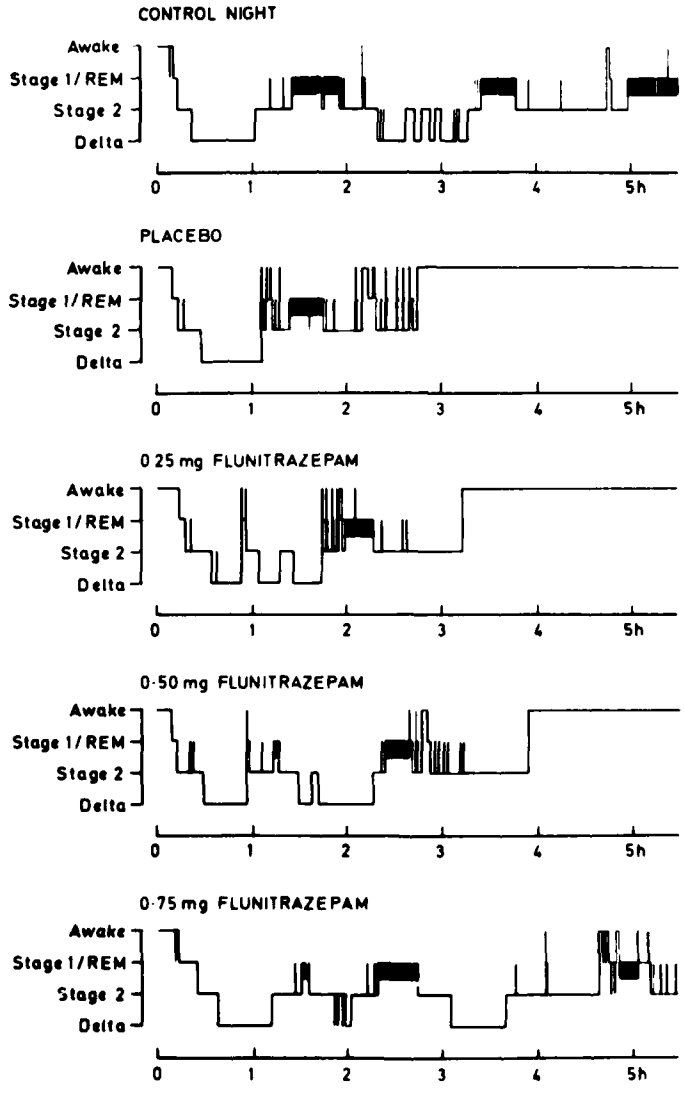

Fig.41 Effect of flunitrazepam (0.25, 0.5 and 0.75 mg) on sleep during the day from 1400 h. With increasing doses daytime sleep approaches the pattern seen at night, and in particular there is an increase in total sleep time

Finally, it must be emphasised that if hypnotics are to be used in the management of sleep difficulties in aircrew a drug with which the individual is familiar must be used. It should be given at the lowest dose, and as infrequently as possible. There should be an interval of 24 h between ingestion and commencement of duty unless their use is closely supervised. Under these circumstances the interval may be reduced to 12 hours. Perhaps it is unnecessary to emphasise that, if hypnotics are to be used in the management of sleep disturbances, the concomitant use of *alcohol is to be avoided.*

Use of Hypnotics by Aircrew

- Must have been used on the ground.
- Use lowest dose.
- Use infrequently.
- Ingestion-duty interval of 24 hours (if under medical supervision – 12 hours).
- Avoid alcohol.

Recommended Hypnotics

1,4-Benzodiazepines

– Diazepam 5–10 mg	To be used only occasionally. Not more than once in 24 hours or twice in 7 days.
– Temazepam 10–20 mg	20 mg may be used daily, if necessary.
30 mg	30 mg may be used occasionally when residual sequelae are not critical.
– Oxazepam 15–30 mg	Useful hypnotic, but poorly absorbed. Suitable when sleep onset not critical.

1,4-Triazolodiazepines

– Triazolam	
0.125–0.25 mg	May be used daily, if necessary.
0.375 mg	May be used occasionally when residual sequelae not critical.
– Brotizolam	
0.125–0.25 mg	May be used daily, if necessary.

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14. Abstract

The inevitable irregularity of work in aircrew is of concern to both civil and military operations, and this handbook is intended for flight medical officers. The relation between alertness and sleep, the nature of sleep in man and his circadian rhythmicity are described, and these factors are discussed in the setting of shiftwork, transmeridian flight and air operations. Disorders of sleep and arousal as they may involve the aeromedical specialist are also covered, and the use of hypnotics discussed.

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